Critical care in case of hemorrhagic stroke

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Epidemiology

- Non-traumatic intracerebral haemorrhage results from rupture of blood vessels in the brain.
- Hemorrhagic Stroke constitutes approximately 13% of all strokes.
- Over 2 million people are affected by intracerebral haemorrhage (ICH) worldwide every year,
- one third of them dying within 1 month,
- and many survivors being left with permanent disability.

Epidemiology

- ICH represents a major global public-health problem
- ICH incidence around the world vary
  - 10-20 per 100,000 per year
- Overall mortality was reported as 26-38%
- Approximately half of this mortality occurs within the first 24 hours

Emergency management

- Stabilization of cardiorespiratory parameters
  - Airway management
  - Blood pressure control
- Hemostatic therapy
- Intracranial pressure monitoring and treatment
- Surgical interventions
- Others(ie,seizure, hyperglicemia)

Airway

- Early neurologic deterioration
- depressed consciousness
- loss of normal reflexes
- unable to protect the airway.
  - Rapidly Endotracheal tube placement (ETT) (Rapid Sequence Intubation)
  - Mechanic ventilation

Airway

- GCS score<8
- deteriorating conscious level
- Risk for aspirating
- No gag reflex
- Respiratory failure

RSI

Airway

- Recommendations for RSI
  - Premedication
    - lidocain (1–2 mg/kg)
  - Induction
    - (etomidat (0.1–0.3 mg/kg) , thiopenthal (1.0–1.5 mg/kg))
  - Neuromusculer paralysis
    - Nondepolarising neuromusculer blocking agents atracurium (0.3-0.5 mg/kg), vecuronium0.01-0.015 mg/kg)
  - Postintubation sedation
    - Propofol (2-3 mg/kg)

Mechanic ventilation (MV)

- Respiratuar rate-tidal volüm
  - pCO_2 about 35 mmHg
  - aggressive hyperventilation (pCO2 < 28 mmHg) can cause vasoconstriction and ischemia.

Blood pressure

- Elevated blood pressure (BP) is common in the acute setting after an ICH.
- Markedly elevated BP levels are associated with hematoma expansion and poor prognosis.
- The management of hypertension immediately after ICH is a matter of debate.
- Issues such as the timing and magnitude of blood pressure lowering are not still resolved.

Table 1. Recent studies of blood pressure control in acute stroke

Study	Design	# Patients	Stroke subtype	Primary finding
Anderson *et al.*, 2010 (INTERACT)	Prospective randomized trial	296	ICH	Hematoma growth is attenuated with rapid, intensive BP reduction after ICH.
ATACH investigators, 2010	Prospective dose-escalation	60	ICH	Rapid, intensive BP reduction after ICH is both feasible and safe.
Beseoglu *et al.*, 2010	Retrospective	105	SAH	Lower maximum SBP, less SBP variation, and higher minimum SBP are associated with improving functional status at discharge after SAH.
Geeganage *et al.*, 2010 (Cochrane)	Meta-analysis	7649	IS, ICH	There was not enough evidence to conclude if BP intervention affects outcome after acute stroke.
Grise *et al.*, 2011	Retrospective	1739	IS	When emergency physicians choose to lower BP in IS, BP is often lowered below recommended treatment thresholds and lowered more rapidly than recommended.
Mayer *et al.*, 2011	Prospective observational	432	SAH, ICH, IS	This study found that minimum recorded blood pressure and excessive blood pressure reduction may contribute to mortality after stroke.
Ntaios *et al.*, 2011 (ASTRAL)	Prospective observational	791	IS	There is a U-shaped relationship between SBP and outcome and an association between outcome and the direction and magnitude of BP change over the first 48 h after stroke.
Ohwaki *et al.*, 2009	Retrospective	100	ICH	The risk of early neurologic deterioration in ICH begins to increase as SBP falls below 123 mmHg.
Pezzini *et al.*, 2011	Prospective observational	264	IS, ICH	Both elevated BP and increased BP variability impact short-term and mid-term outcome in patients with ICH, and less so in IS.
Robinson *et al.*, 2010 (COSSACS)	Prospective randomized trial	763	IS, ICH	Although continuing antihypertensives after acute stroke reduced BP, there was no significant difference in 2-week death or dependency in this underpowered study.
Sandset *et al.*, 2011 (SCAST)	Prospective randomized trial	2004	IS, ICH	Although underpowered, there was a trend toward increased vascular events and worsening functional outcome in patients started on candesartan after acute stroke.

ICH, intracerebral hemorrhage; IS, ischemic stroke; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure.

Effects of Early Intensive Blood Pressure-Lowering Treatment on the Growth of Hematoma and Perihematomal Edema in Acute Intracerebral Hemorrhage

The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT)

Craig S. Anderson, MD; Yining Huang, MD; Hisatomi Arima, MD; Emma Heeley, PhD; Christian Skulina, MD; Mark W. Parsons, MD; Bin Peng, MD; Qiang Li, BSc; Steve Su, PhD; Qing Ling Tao, MD; Yue Chun Li, MD; Jian Dong Jiang, MD; Li Wen Tai, MD; Jin Li Zhang, MD; En Xu, MD; Yan Cheng, MD; Lewis B. Morgenstern, MD; John Chalmers, MD; Ji Guang Wang, MD; for the INTERACT Investigators

Neurologic Critical Care

Antihypertensive treatment of acute cerebral hemorrhage*

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators

Objective: To determine the feasibility and acute (i.e., within 72 hrs) safety of three levels of systolic blood pressure reduction in subjects with supratentorial intracerebral hemorrhage treated within 6 hrs after symptom onset.

Design: A traditional phase I, dose-escalation, multicenter oversight on subject safety. Each subject was followed-up for 3 months to preliminarily assess mortality and the clinical outcomes. A total of 18, 20, and 22 patients were enrolled in the respective three tiers of systolic blood pressure treatment goals. Overall, 9 of 60 patients had treatment failures (all in the last tier).

AHA recommendations

Table 4. Recommended guidelines from the American Heart Association for treating elevated blood pressure in spontaneous intracranial hemorrhage

If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 mins
If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg
If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (e.g., MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure; clinically reexamine the patient every 15 mins

ICP, intracranial blood pressure; MAP, mean arterial blood pressure; SBP, systolic blood pressure.
Adapted from Broderick et al: *Circulation* 2007, 116:e391–e413 (1).

AHA recommendations

Table 5. Intravenous medications that may be considered for control of elevated blood pressure in patients with intracranial hemorrhage as recommended by the American Heart Association

Drug	Intravenous Bolus Dose	Continuous Infusion Rate
Labetalol	5–20 mg every 15 mins	2 mg min^{-1} (maximum 300 mg/day)
Nicardipine	NA	5–15 mg hr^{-1}
Esmolol	250 μg kg^{-1} IVP loading dose	25–300 μg kg^{-1} min^{-1}
Enalapril	1.25–5 mg IVP every 6 hrs[a]	NA
Hydralazine	5–20 mg IVP every 30 mins	1.5–5 μg kg^{-1} min^{-1}
Nipride (140, 141)	NA	0.1–10 μg kg^{-1} min^{-1}

IVP, intravenous push; NA, not applicable.

[a]Because of the risk of precipitous blood pressure lowering, the first test dose for enalapril should be 0.625 mg. Adapted from Broderick et al: *Circulation* 2007; 116:e391–e413 (1).

EUSI recommendations

Recommendations from EUSI for blood pressure management in ICH.

Previous history of HTN	Gradually reduce MAP to <120 but >84 mm Hg; avoid a reduction of >20%. BP limit is <180/105 mm Hg, if treatment is necessary target should be <160/100 mm Hg.
No history of HTN	Reduce MAP to 110 mm Hg. BP limit is <160/95 mm Hg, if treatment is necessary target should be <150/90 mm Hg.
When increased ICP is present	Adapt MAP and BP limits to target a CPP of 60–70 mm Hg.

EUSI guidelines for the management of blood pressure.

HTN= hypertension; MAP: mean arterial pressure; BP: blood pressure; ICP: intracranial pressure; CPP: cerebral perfusion pressure.

Haemostatic therapy

- oral anticoagulants (OACs) use
- acquired or congenital coagulation factor deficiencies
- qualitative or quantitative platelet abnormalities

Haemostatic therapy

- Warfarin therapy increases the risk of ICH 5-10 times
- ~15% of ICH are associated with warfarin use

- Unless INR is rapidly normalised (<1.4) increases progressive bleeding and clinical deterioration

What have we got?

- Conventional
  - FFP (fresh frozen plasma)
  - Vitamin K
- Potential
  - PPCs (prothrombin complex concentrates)
  - rFVIIa (recombinant activated factor VII)

FFP

- 10-20 mL/kg iv inf.
- Disadvantages
  - transfusion reactions
  - processing time
  - volume load in cardiac and renal failure

Vit-K

- 10 mg of vitamin K_1 by slow intravenous infusion
- It carries the risk of hypotension and anaphylaxis
- It takes at least 6 hours to normalize the INR
- vitamin K is suitable for the supplemental therapy

PCCs

- PCCs are plasma-derived factor concentrates.
- They are primarily used to treat factor IX deficiency.
- PCCs contain factors II, VII, and X in addition to IX

PCCs

- 15-50 units/kg
- rapid reconstitution and administration
- High concentrations of coagulation factors in small volumes
- PCCs can rapidly normalize INR (within minutes) in patients taking OACs

Use of Factor IX Complex in Warfarin-related Intracranial Hemorrhage

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Abstract

OBJECTIVE: Anticoagulation-treated patients presenting with intracranial hemorrhage, including subdural hematoma, epidural hematoma, subarachnoid hemorrhage, and intracerebral hemorrhage, require urgent correction of their coagulopathy to prevent worsening hemorrhage and to facilitate surgical intervention when necessary. In this study, we compared the use of fresh frozen plasma (FFP) with that of Factor IX complex concentrate (FIXCC) to achieve rapid correction of warfarin anticoagulation.

METHODS: Patients admitted to a tertiary care center with computed tomography-proven intracranial hemorrhage and a prothrombin time of more than 17 seconds were considered for inclusion in the study protocol. Complete data sets were obtained for eight patients randomized to treatment with FFP and five patients randomized to treatment with FFP supplemented with FIXCC. The prothrombin time and International Normalized Ratio were measured every 2 hours for 14 hours. Correction of anticoagulation was defined as an International Normalized Ratio of <=1.3.

RESULTS: A difference in repeated International Normalized Ratio measurements during the first 6 hours of correction was observed between the FIXCC and FFP groups (**P**< 0.03). The rate of correction was greater (**P**< 0.01) and the time to correction was shorter (**P**< 0.01) for the FIXCC-treated group. No difference in neurological outcomes was detected between groups, but a higher complication rate was observed for the FFP-treated group.

CONCLUSION: The use of FIXCC accelerated correction of warfarin-related

Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding

A Randomized, Plasma-Controlled, Phase IIIb Study

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Background—Patients experiencing major bleeding while taking vitamin K antagonists require rapid vitamin K antagonist reversal. We performed a prospective clinical trial to compare nonactivated 4-factor prothrombin complex concentrate (4F-PCC) with plasma for urgent vitamin K antagonist reversal.

Methods and Results—In this phase IIIb, multicenter, open-label, noninferiority trial, nonsurgical patients were randomized to 4F-PCC (containing coagulation factors II, VII, IX, and X and proteins C and S) or plasma. Primary analyses examined whether 4F-PCC was noninferior to plasma for the coprimary end points of 24-hour hemostatic efficacy from start of infusion and international normalized ratio correction (≤1.3) at 0.5 hour after end of infusion. The intention-to-treat efficacy population comprised 202 patients (4F-PCC, n=98; plasma, n=104). Median (range) baseline international normalized ratio was 3.90 (1.8–20.0) for the 4F-PCC group and 3.60 (1.9–38.9) for the plasma group. Effective hemostasis was achieved in 72.4% of patients receiving 4F-PCC versus 65.4% receiving plasma, demonstrating noninferiority (difference, 7.1% [95% confidence interval, –5.8 to 19.9]). Rapid international normalized ratio reduction was achieved in 62.2% of patients receiving 4F-PCC versus 9.6% receiving plasma, demonstrating 4F-PCC superiority (difference, 52.6% [95% confidence interval, 39.4 to 65.9]). Assessed coagulation factors were higher in the 4F-PCC group than in the plasma group from 0.5 to 3 hours after infusion start ($P<0.02$). The safety profile (adverse events, serious adverse events, thromboembolic events, and deaths) was similar between groups; 66 of 103 (4F-PCC group) and 71 of 109 (plasma group) patients experienced ≥1 adverse event.

Conclusions—4F-PCC is an effective alternative to plasma for urgent reversal of vitamin K antagonist therapy in major bleeding events, as demonstrated by clinical assessments of bleeding and laboratory measurements of international normalized ratio and factor levels.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00708435.

(***Circulation***. **2013;128:1234-1243.**)

Key Words: anticoagulants ■ hemorrhage ■ plasma ■ prothrombin complex concentrates ■ vitamin K antagonist

Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists

A meta-analysis

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Summary

Prothrombin complex concentrates (PCCs) are recommended as the treatment of choice in warfarin-related coagulopathy. However, the risk of thromboembolic complications associated with their use is not well defined. We performed a meta-analysis to estimate the rate of thromboembolic complications in patients receiving vitamin K antagonists (VKAs) treated with PCCs for bleeding or before urgent surgery. Medline and Embase databases were searched. Two reviewers performed study selection and extracted data independently. Studies providing data on incidence of thromboembolic complications in VKA-treated patients were eligible for the study. Weighted mean proportion of the rate of thromboembolic complications and the mortality rate were calculated. Twenty-seven studies (1,032 patients) were included. Seven studies used 3-factor, and 20 4-factor PCCs. Twelve patients had a thromboembolic complication (weighted mean 1.4%; 95% CI 0.8–2.1), of which two were fatal. The incidence of thromboembolic events was 1.8% (95% CI 1.0–3.0) in patients treated with 4-factor PCCs, and 0.7% (95% CI 0.0–2.4) in patients treated with 3-factor PCCs. Total mortality rate was 10.6% (95% CI 5.9–16.6). In conclusion, our results suggest there is a low but quantifiable risk of thromboembolism in VKA-treated patients receiving PCCs for anticoagulation reversal. These findings should be confirmed in randomised, controlled trials.

Keywords

Prothrombin complex concentrates, PCC, coumarins, thromboembolic complications, haemorrhage

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rFVIIa

- rFVIIa licensed to treat hemophilia patients with congenital factor VII deficiency
- It has garnered attention as a potential treatment for spontaneous and OAC-associated ICH.
  - Mayer, S. A. *et al.* Efficacy and safety of recombinant activated factor vII for acute intracerebral hemorrhage. *N. Engl. J. Med.* 358, 2127–2137 (2008).
  - Mayer, S. A. *et al.* Recombinant activated factor vII for acute intracerebral hemorrhage. *N. Engl. J. Med.* 352, 777–785 (2005).

rFVIIa

- normalise the INR within minutes (10μg/kg to 90 μg/kg)
- it expedites neurosurgical intervention
- rFVIIa should be used as an adjunct to coagulation-factor replacement and vitamin K because the effect will last only several hours

Hematoma enlargement

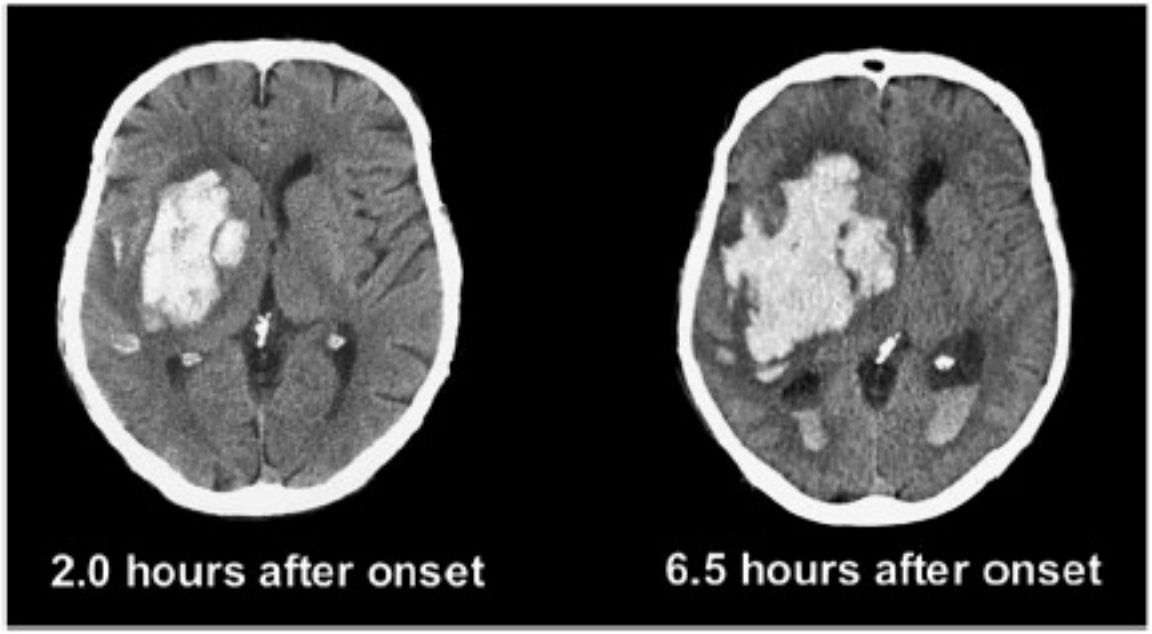

Fig. 1. Early hematoma growth in a 48 year-old chronically hypertensive woman. Left: The baseline CT scan performed shows a moderate-sized right putamen ICH. At this point she is stuporous with a left hemiparesis. Right: A follow up CT performed after she deteriorated to coma with bilateral decerebrate posturing shows massive expansion of the hematoma, as well as new intraventricular hemorrhage and obstructive hydrocephalus. Within 24 h she was declared brain dead. From Mayer SA, Rincon F. Treatment of Intracerebral Hemorrhage. Lancet 2005, with permission.

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Reducing the risk of ICH enlargement

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Abstract

Intracerebral hemorrhage (ICH) comprises 15% of all strokes, and carries the highest risk of mortality and poor long-term outcome. ICH has long been recognized as the least treatable form of stroke, and hematoma volume as the strongest single predictor of mortality and outcome. CT-based studies have found that early substantial hematoma expansion occurs in 18–38% of patients initially scanned within 3 h of symptom onset. This finding is associated with early neurological deterioration and an increased risk of poor outcome. Ultra-early hemostatic therapy might be beneficial in preventing hematoma growth, resulting in improved mortality and neurological function. Recombinant activated factor VII (rFVIIa) promotes local hemostasis in the presence or absence of coagulopathy at sites of vascular injury, and is a promising treatment for arresting active bleeding in ICH. The safety and feasibility of this approach was confirmed in a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial of 399 patients with non-coagulopathic ICH. Administration of rFVIIa within 4 h of ICH onset resulted in a significant reduction of hematoma expansion at 24 h, and reduced mortality and improved functional outcome at 90 days. A confirmatory phase III trial (The FAST Trial) to confirm these results will complete enrollment in the end of 2006.

Keywords: Intracerebral hemorrhage; Recombinant factor VIIa; Hematoma growth; Hemostatic therapy; Early therapy; Outcome

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Review

A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute intracerebral hemorrhage without hemophilia

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ABSTRACT

Hematoma growth is common in intracerebral hemorrhage (ICH) and is associated with a poor outcome for patients. To evaluate the efficacy and safety of recombinant activated factor VII (rFVIIa) used as a hemostatic agent in patients with ICH without hemophilia, we searched Medline, Scopus, the Cochrane Library, Clinicaltrials.gov and the Stroke Trials Directory. Five randomized controlled trials were selected for analysis. Although rFVIIa can reduce the change in ICH volume, there was no significant difference in mortality, modified Rankin Scale (mRS) score or extended Glasgow Outcome Scale (GOS-E) score in patients treated with rFVIIa or placebo. There was a significant increase in arterial thromboembolic adverse events (TAE) in patients treated with rFVIIa. There was an increase in deep vein thrombosis in patients with spontaneous ICH and traumatic ICH. In conclusion, the use of rFVIIa reduces the growth of the hematoma but does not improve patient survival or functional outcome after ICH; in addition, rFVIIa increases the incidence of arterial TAE.

AHA 2010 recommendations

- **Severe coagulation factor deficiency or severe thrombocytopenia**
  - **appropriate factor replacement therapy or platelets, *(Class I;LOE: C)***
- **ICH whose INR is elevated due to OACs**
  - **warfarin withheld**
  - **replace vitamin K–dependent factors**
  - **receive intravenous vitamin K (Class I; LOE: C)**
  - **PCCs are reasonable to consider as an alternative to FFP (Class IIa; LOE: B)**
  - **rFVIIa is not routinely recommended as a sole agent for OAC reversal in ICH (Class III; LOE: C).**
  - **rFVIIa is not recommended in unselected patients. (Class III; LOE: A)**

- When it could be restarted full anticoagulation safely?
  - 10–14 days after ICH

ICP monitoring

- Patients with a GCS score of <8,
- those with clinical evidence of transtentorial herniation, or
- those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment.
- A cerebral perfusion pressure of 50 to 70 mm Hg may be reasonable to maintain depending on the status of cerebral autoregulation *(Class IIb; LOE:C)*. (New recommendation)

Elevated ICP

- In patients who present acutely with clinical signs of brainstem herniation
  - Elevation of head (30-45 degrees)
  - 20% mannitol iv infusion (1.0-1.5 mg/kg)
  - Hyperventilation (pCO_2 28-32 mmHg)
- definitive neurosurgical procedure
  - placement of an ICP monitor
  - craniotomy
  - ventriculostomy

Elevated ICP

- Position
  - Head elevation (30 degrees)
- Fluids
  - Isotonic fluids
  - 20% mannitol
  - 3% hypertonic saline

Isotonic fluids

- 0.9% saline, 1mL/kg/h, standard intravenous replacement fluid
- Euvolemia should be maintained
- Solutions containing dextrose should be avoided unless hypoglycaemia is present

3% hypertonic salin

- increasingly use
- in patients with significant perihaematomal oedema and mass effect
- 1 mL/kg/h
- The goal; baseline state of hyperosmolality (300–320 mmol/kg) and hypernatraemia (150–155 mEq/L)

3% hypertonic saline

- Infusion therapy should not be discontinued suddenly.
- Rebound edema and ICP elevation !
- Sodium should not be reduced more rapid than 12 mEq/L within 24 hours.

Seizure

- Risk ~8%/30 days
- Convulsive status epilepticus 1-2%
- Lobar location !
- Treatment
  - Lorazepam 0.05–0.10 mg/kg iv (acute treat.) followed by,
  - Phenytoin (15–20 mg/kg)
  - Fosphenytoin (15–20 mg/kg)
  - Valproic acid (15–45 mg/kg)
  - Phenobarbital (15–20 mg/kg)

loading

Seizure

- Prophylactic AED?
- Nonconvulsive seizures or status epilepticus
- monitor with electroencephalography for at least 48 h
- treat nonconvulsive seizures with midazolam (starting dose 0·2 mg/kg/h)

AHA 2010

- Clinical seizures should be treated with antiepileptic drugs *(Class I; LOE: A)*
- Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury *(Class IIa; LOE: B)*.
- Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs *(Class I; LOE: C)*
- Prophylactic anticonvulsant medication should not be used *(Class III; LOE:B)*

Fever

- associated with poor outcome, neuronal injury and death
- Paracetamol
- Cooling
  - Adhesive surface-cooling systems
  - Endovascular heat-exchange catheters
- therapeutic cooling (or induced hypothermia) has not been systematically investigated in ICH patients.

Glycemia

- Hyperglycemia
  - cerebral ischemic injury
  - increased 30-day mortality

- Declining glucose values after ICH
  - decreased risk of hematoma expansion
  - early glucose control may improve outcomes
- Glucose levels should be treated in the acute phase after ICH >180 mg/dL

AHA 2010

- Glucose should be monitored and normoglycemia is recommended *(Class I: LOE: C)*.

(New recommendation)

Others

- Anemia
- Nutrition
- Venous thrombosis prophylaxis

Anemia

Anemia and hematoma volume in acute intracerebral hemorrhage

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Objective: Anemia increases risk of bleeding complications in the critically ill. In primary intracerebral hemorrhage (ICH), the most fatal type of stroke, outcome is largely dependent on the volume of hemorrhage into the brain. We investigated the relationship between anemia and clinical course of acute ICH.

Methods: Six hundred ninety-four consecutive subjects were identified from an ongoing single-center prospective cohort study of nontraumatic ICH during a 6-year period. Anemia was defined according to World Health Organization criteria. Study end points were ICH volume, as measured on the baseline computed tomography scan, and 30-day mortality.

Results: Anemia was present in 177 (25.8%) patients on admission. Patients with anemia were older ($p = 0.005$) and more likely to have coronary artery disease ($p < 0.0001$). In multivariable analysis, anemia ($p = 0.009$), lobar location of ICH ($p < 0.001$), white blood cell count ($p < 0.001$), and admission diastolic blood pressure ($p < 0.001$) were associated with larger ICH volume. Although after accounting for ICH volume, none of these variables was a significant predictor of 30-day mortality in multivariable analysis, the size of the marginal reduction in the odds ratio for anemia suggests that it may have a small effect on mortality through mechanisms in addition to ICH volume.

Conclusions: Anemia is common in acute ICH and its presence at admission is an independent predictor of larger volume of ICH. Given the central role of ICH volume in outcome, clarification of the mechanisms underlying this relationship may offer novel therapeutic targets for reducing ICH morbidity and mortality. (Crit Care Med 2009; 37:1442–1447)

KEY WORDS: anemia; inflammation; blood pressure; cerebral hemorrhage; intensive care unit

Anemia

Critical Care

CRITICAL CARE

Anemia is an independent prognostic factor in intracerebral hemorrhage: an observational cohort study

Critical Care 2013, **17**:R148 doi:10.1186/cc12827

Results: Overall short-term-outcome was worse in anemic patients (mRS[4-6] OAA = 93.3% vs. non-OAA = 61.2%, $P<0.01$), and there was a further shift towards an increased long-term mortality ($P = 0.02$). The probability of unfavorable long-term-outcome (mRS[4-6]) in OAA was elevated 7-fold (OR:7.5; $P<0.01$). Receiver operating characteristics curve (ROC) analysis revealed a positive but poor association of ICH-volume and anemia (AUC = 0.67) suggesting volume-undriven outcome-effects of anemia (AUC = 0.75). Multivariate regression analyses revealed that anemia, besides established parameters, has the strongest relation to unfavorable outcome (OR:3.0; $P<0.01$). This is even more pronounced in minor-volume-ICH (OR:5.6; $P<0.01$).

Nutrition

Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial

Lancet 2005; 365: 764–72

See Comment

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*The FOOD Trial Collaboration**

Summary

Background Undernutrition is common in patients admitted with stroke. We aimed to establish whether the timing and route of enteral tube feeding after stroke affected patients' outcomes at 6 months.

Methods The FOOD trials consist of three pragmatic multicentre randomised controlled trials, two of which included dysphagic stroke patients. In one trial, patients enrolled within 7 days of admission were randomly allocated to early enteral tube feeding or no tube feeding for more than 7 days (early versus avoid). In the other, patients were allocated percutaneous endoscopic gastrostomy (PEG) or nasogastric feeding. The primary outcome was death or poor outcome at 6 months. Analysis was by intention to treat.

Findings Between Nov 1, 1996, and July 31, 2003, 859 patients were enrolled by 83 hospitals in 15 countries into the early versus avoid trial. Early tube feeding was associated with an absolute reduction in risk of death of 5·8% (95% CI −0·8 to 12·5, p=0·09) and a reduction in death or poor outcome of 1·2% (−4·2 to 6·6, p=0·7). In the PEG versus nasogastric tube trial, 321 patients were enrolled by 47 hospitals in 11 countries. PEG feeding was associated with an absolute increase in risk of death of 1·0% (−10·0 to 11·9, p=0·9) and an increased risk of death or poor outcome of 7·8% (0·0 to 15·5, p=0·05).

Interpretation Early tube feeding might reduce case fatality, but at the expense of increasing the proportion surviving with poor outcome. Our data do not support a policy of early initiation of PEG feeding in dysphagic stroke patients.

[Intervention Review]

Interventions for dysphagia and nutritional support in acute and subacute stroke

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Swallowing therapy: acupuncture, drug therapy, neuromuscular electrical stimulation, pharyngeal electrical stimulation, physical stimulation (thermal, tactile), transcranial direct current stimulation, and transcranial magnetic stimulation each had no significant effect on case fatality or combined death or dependency. Dysphagia at end-of-trial was reduced by acupuncture (number of studies (t) = 4, numbers of participants (n) = 256; OR 0.24; 95% CI 0.13 to 0.46; P < 0.0001; I^2 = 0%) and behavioural interventions (t = 5; n = 423; OR 0.52; 95% CI 0.30 to 0.88; P = 0.01; I^2 = 22%). Route of feeding: percutaneous endoscopic gastrostomy (PEG) and nasogastric tube (NGT) feeding did not differ for case fatality or the composite outcome of death or dependency, but PEG was associated with fewer treatment failures (t = 3; n = 72; OR 0.09; 95% CI 0.01 to 0.51; P = 0.007; I^2 = 0%) and gastrointestinal bleeding (t = 1; n = 321; OR 0.25; 95% CI 0.09 to 0.69; P = 0.007), and higher feed delivery (t = 1; n = 30; MD 22.00; 95% CI 16.15 to 27.85; P < 0.00001) and albumin concentration (t = 3; n = 63; MD 4.92 g/L; 95% CI 0.19 to 9.65; P = 0.04; I^2 = 58%). Although looped NGT versus conventional NGT feeding did not differ for end-of-trial case fatality or death or dependency, feed delivery was higher with looped NGT (t = 1; n = 104; MD 18.00%; 95% CI 6.66 to 29.34; P = 0.002). Timing of feeding: there was no difference for case fatality, or death or dependency, with early feeding as compared to late feeding. Fluid supplementation: there was no difference for case fatality, or death or dependency, with fluid supplementation. Nutritional supplementation: there was no difference for case fatality, or death or dependency, with nutritional supplementation. However, nutritional supplementation was associated with reduced pressure sores (t = 2; n = 4125; OR 0.56; 95% CI 0.32 to 0.96; P = 0.03; I^2 = 0%), and, by definition, increased energy intake (t = 3; n = 174; MD 430.18 kcal/day; 95% CI 141.61 to 718.75; P = 0.003; I^2 = 91%) and protein intake (t = 3; n = 174; MD 17.28 g/day; 95% CI 1.99 to 32.56; P = 0.03; I^2 = 92%).

Venous thrombosis prophylaxis

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SHORT REPORT

Early heparin therapy in patients with spontaneous intracerebral haemorrhage

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Abstract

In 68 patients with spontaneous intracerebral haemorrhage the effect of heparin treatment beginning on the second, fourth or tenth day was investigated. Early (day 2) low-dose heparin medication significantly lowered the incidence of pulmonary embolism. An increase in the number of patients with rebleeding was not observed. The results indicate that the early use of heparin in these patients is safe and can be recommended for the prevention of thromboembolic complications.

of deep-vein thromboses and pulmonary emboli. Therefore, an additional group of 22 patients received heparin in the same dose but starting on the second day following the vascular accident. The design of the study accords with the recommendations of the Helsinki Convention of 1975 and was carried out with the approval of the Ethics Committee of the University of Goettingen School of Medicine.

The patients' biographical data as well as their clinical classification according to the HUNT and HESS scale[3] are shown in table 1. The diagnosis of ICH was substantiated within 24 hours in all 68 patients using CT.

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- Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings *(Class I;LOE: B)*
- After documentation of cessation of bleeding, lowdose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset *(ClassIIb; LOE: B)*

Surgical treatment

- Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible *(Class I; LOE: B)*
- Initial treatment of these patients with ventricular drainage alone rather than surgical evacuation is not recommended (*Class III; LOE: C)*
- The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational *(Class IIb;LOE: B)*

Thank you for your attention