Advances in critical care/emergency medicine 2013

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DOI: https://doi.org/10.1161/STROKEAHA.113.004223

Advances in Critical Care and Emergency Medicine

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Formatiert: Englisch (USA)

Of the many publications in this field, the following appear to be most relevant for clinical practice.

Ischemic Stroke

Intravenous thrombolysis with tissue plasminogen activator (tPA) is the only therapy proven to improve outcome in ischemic stroke. Studies of intravenous thrombolysis show that therapy response is time dependent; the sooner patients receive tPA after stroke onset, the better the chance of good outcome.{Marler, 2000 #393;Lees, 2010 #372} The required brain imaging before tPA administration and further imponderables delay the therapy initiation. In the Pre-Hospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) pilot study, Weber and colleagues attempt to speed up the process by administering tPA prior to hospital arrival. {Weber, 2013 #366} If patients with a high probability of stroke contacted the emergency medical system within 4 hours after symptom onset, a stroke emergency mobile unit (STEMO) equipped with a CT scanner was dispatched. Brain imaging was performed at the scene (along with point of care blood work) enabling tPA administration in the STEMO. For STEMO patients the median time between emergency call and tPA initiation was 58 minutes (5-63), for a group of historic controls 92 (79-112). The PHANTOM-S study was a non-randomized pilot study done in urban Germany (Berlin). A randomized controlled study done in a more rural region of Germany (Homburg) showed a similar relative time decrease when using a CT-equipped STEMO, while the initiation of tPA therapy after emergency notification occurred more quickly in both groups.{Walter, 2012 #360} Both studies suggest that a CT-equipped STEMO decreases the time to tPA administration, which may be of significant clinical benefit.

Hyperglycemia is associated with worse stroke outcome, but there is no evidence that strict glucose control improves outcome.{Kruyt, 2010 #499} In a proof of concept study to determine if aggressive glucose management could attenuate infarct growth, patients with carotid territory strokes were randomized to intensive insulin therapy (IIT; N=87) or standard (subcutaneous) insulin therapy (SIT; N=89) within 6 hours after symptom onset.{Rosso, 2012 #404} In the IIT group, insulin was administered as a continuous infusion with a goal glucose <7 mmol/L (<126 mg/dL) for a duration of 24 hours. MRIs were obtained within 5 hours after onset (before randomization) and again after therapy cessation (1 to 3 days after stroke onset). While the IIT regimen improved glucose control, it was associated with increased infarct growth. The IIT regimen was also associated with increased hypoglycemia episodes. Clinical outcomes were similar between the treatment groups. The ongoing Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial opts for a similar glucose goal (80-130 mg/dL) but allows for 12 hours between symptom onset and treatment onset.{Southerland, 2012 #420} Unless the results of SHINE suggest otherwise, the data abundance suggests that intensive insulin therapy in acute stroke is of no benefit and may cause harm.{Bellolio, 2011 #448}

Intracerebral Hemorrhage

After INTERACT1, the larger INTERACT2 trial aimed at investigating whether rapid lowering of blood pressure (target systolic level <140 mm Hg within 1 hour of randomization and maintained for 7 days) {Anderson, 2013 #7} improves the outcome in patients with intracerebral hemorrhage (ICH) compared to current guideline-recommended treatment (target systolic level of <180 mm Hg) {Morgenstern, 2010 #8}. Patients were treated within 6 hours after symptom onset; exclusion criteria included structural bleeding causes, deep coma (median GCS 14), massive hematomas (median volume 11 cc), poor prognosis and plans for immediate surgery. Among 2794 patients for whom the primary outcome (modified Rankin Scale) after 90 days could be determined, average blood pressure at enrollment was 179/101 mmHg. Systolic blood pressure after 1 hour and 6 hours treatment was 150 mmHg and 139 mmHg with intensive therapy *versus* 164 mmHg and 153 mmHg with conventional treatment. The primary outcome (death or major disability) was not different between groups. The ordinal analysis of modified Rankin scores, however, indicated that participants in the intensive treatment group had significantly improved functional outcomes with better overall health-related quality (EQ-5D score; *P*=0.002). Several limitations of INTERACT2 are noted, among them e.g. the fact that antihypertensive medication was not standardized in the acute phase and that clinical management probably differed among participating centers. The ongoing trial ATACH II will provide further data on intensive lowering of blood pressure within 4.5 hours using intravenous nicardipine.{Qureshi, 2011 #9} Despite the negative primary endpoint, INTERACT2 shows that rapid blood pressure lowering is safe and may improve functional outcome in a selected subgroup of patients with relatively mild symptoms/small hemorrhages. Targeting systolic blood pressure values <140 mm Hg is justifiable in this specific patient population with spontaneous non-structural ICH.

The Surgical Trial in Lobar Intracerebral Hemorrhage (STICH) II compared early surgery with initial conservative treatment in an international, multicenter, prospective, randomized trial.{Mendelow, 2013 #15} Only conscious patients with superficial lobar intracerebral hemorrhage of 10-100 mL and no intraventricular hemorrhage, admitted within 48 hours after symptom onset, were included. In the group randomized to initial conservative treatment, delayed evacuation was permitted if judged clinically appropriate. Of the 601 patients enrolled, 307 were randomly assigned to early surgery and 294 to initial conservative treatment. Unfavorable outcome (based on extended Glasgow Outcome Score) was seen in 59% of the early surgery group patients and in 62% of the initial conservative treatment group (OR 0.86; *P*=0.367). Eventually, 21% of the patients randomized to initial conservative treatment underwent surgery. The absence of a significant difference between the groups may be related to the heterogeneous patient population (*i.e.* hematoma volumes ranging from 10-100 mL), a high crossover rate from initial conservative treatment to surgery and the lack of standardized procedures for both the surgical intervention and the conservative treatment. Early surgery may be only one important piece in the treatment of patients with ICH. The ongoing Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR-IVH) and Minimally Invasive Surgery plus tPA for ICH Evacuation (MISTIE) trials will show whether minimal invasive techniques will play a role in the treatment of subsets of ICH patients.

Cardiac Arrest

Since two seminal studies showed that hypothermia improves outcome, hypothermia is part of the standard treatment of patients with cardiac arrest due to ventricular

fibrillation (VF).{Bernard, 2002 #852;, 2002 #881} It has been hypothesized that earlier cooling would be associated with better outcome. In a study by Kim and colleagues, patients with cardiac arrest were randomized to pre-hospital cooling with infusion of chilled (4°C) saline *versus* standard of care over a 5 year period.{Kim, 2013 #750} The study included all patients with cardiac arrest regardless of initial rhythm. Goal temperature for cooling was ≤34°C. The primary analysis included 1359 patients. For patients who also received hospital cooling, administration of cooled saline in the pre-hospital setting, reduced the time to goal temperature by over an hour (4.2 hours versus 5.5 hours; $P<0.001$). Pre-hospital cooling, however, did not result in decreased mortality or improved neurological outcome at the time of hospital discharge. Besides, these patients were also more likely to suffer a re-arrest and have evidence of pulmonary edema upon hospital admission. A separate study actually questions the benefit of hypothermia treatment in patients with out of hospital cardiac arrest.{Nielsen, 2013 #768} In a randomized controlled study comparing two temperature goals, Nielsen and colleagues found no decrease in mortality or improvement in neurological outcome in patients randomized to hypothermia (33°C) compared to those where the focus was to avoid fever (36°C). Overall, these trials suggest that decreasing the time to achieve hypothermia, i.e. earlier cooling confers no benefit. Moreover, the benefit of hypothermia itself is questioned. Further studies will be needed to determine the true value of hypothermia, appropriate temperature targets and the duration of therapy.

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