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the many publications in this field, the ones discussed hereunder seem 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 response to therapy is time-dependent; the sooner the patients receive tPA, the better the chance of good outcome. The intensive insulin therapy arm (N=89) <6 hours after symptom onset. The required brain imaging before tPA administration delays the initiation of therapy because it necessitates patient transport. In the Pre-Hospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) pilot study, Weber et al. attempt to speed up stroke treatment by administering tPA before hospital arrival. When patients with presumed stroke contacted the emergency medical system, a stroke emergency mobile unit equipped with a CT scanner was dispatched. Brain imaging was performed at the scene, enabling tPA administration in the stroke emergency mobile unit. For patients in stroke emergency mobile unit, the median time between emergency call and initiation of tPA was 58 minutes (5–63); this time was 92 minutes (79–112) in a group of historic controls. The PHANTOM-S study was a nonrandomized study performed in urban Germany. A randomized controlled study performed in a more rural region of Germany showed a similar relative decrease in the time to tPA treatment among patients treated in a CT-equipped mobile stroke unit compared with those treated in the emergency room. These studies show that CT-equipped mobile stroke units decrease the time to tPA administration, which could translate into significant clinical benefit.

Hyperglycemia is associated with worse stroke outcomes, but there is no evidence that strict glucose control improves outcome. 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 (N=87) or standard (subcutaneous) insulin therapy (N=89) <6 hours after symptom onset. In the intensive insulin therapy group, insulin was administered as a continuous infusion with a goal glucose <7 mmol/L (<126 mg/dL) for a duration of 24 hours. MR images were obtained <5 hours after onset (before randomization) and again after cessation of therapy. Although the intensive insulin therapy regimen improved glucose control, it was associated with increased infarct growth. The intensive insulin therapy regimen also led to an increase in hypoglycemia episodes. Clinical outcomes were similar between the treatment groups. The ongoing Stroke Hyperglycemia Insulin Network Effort (SHINE) trial aims for a similar glucose goal in the intensive treatment arm (80–130 mg/dL), but allows for 12 hours between symptom onset and initiation of treatment. Notwithstanding SHINE, the abundance of data to date suggest that intensive insulin therapy in acute stroke is of no benefit and may cause harm.

Intracerebral Hemorrhage

After the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT1) pilot study, the larger INTERACT2 study tested whether rapid lowering of blood pressure (target systolic <140 mm Hg) was justifiable in patients with intracerebral hemorrhage (ICH) compared with current guideline-recommended treatment (target systolic <180 mm Hg). Patients were treated <6 hours after symptom onset; exclusion criteria included structural causes for bleeding, deep coma (median Glasgow Coma Scale, 14), massive hematomas (median volume, 11 mL), poor prognosis, and plans for immediate surgery. Among 2794 patients for whom the primary outcome (modified Rankin Scale) could be determined at 90 days, average enrollment blood pressure was 179/101 mm Hg, Systolic blood pressure 1 and 6 hours after treatment was 150 and 139 mm Hg with intensive therapy versus 164 and 153 mm Hg with conventional treatment. The primary outcome (death or major disability) did not differ between groups. Ordinal analysis of modified Rankin Scale 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). Limitations of INTERACT2 are noted; particularly neither antihypertensive medication nor clinical management was standardized in the acute phase. The ongoing Antihypertensive Treatment of Cerebral Hemorrhage (ATACH II) trial will provide further data on intensive lowering of blood pressure <4.5 hours using intravenous nicardipine. Despite the negative primary end point, INTERACT2 shows that rapid blood pressure lowering is safe and may improve functional outcome in a select subgroup of patients with relatively mild symptoms/small hemorrhages. Targeting a systolic blood pressure value <140 mm Hg is justifiable in this patient population with spontaneous ICH.

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The Surgical Trial in Lobar Intracerebral Hemorrhage (STICH) II study compared early surgery with initial conservative treatment in an international multicenter trial. Only conscious patients with superficial lobar ICH between 10 to 100 mL and no intraventricular hemorrhage admitted <48 hours after symptom onset were included. Of the 601 patients enrolled, 307 were randomly assigned to early surgery and 294 to initial conservative treatment. In the group randomized to initial conservative treatment, delayed evacuation was permitted if judged clinically appropriate. Unfavorable outcome (based on extended Glasgow Outcome Scale) was seen in 59% of the early surgery group patients and in 62% of the initial conservative treatment group (odds ratio, 0.86; \( P=0.367 \)). Of the patients randomized to initial conservative treatment, 21% eventually went on to surgery. The absence of a significant difference between the groups may be related to the heterogeneous patient population (ie, hematoma volumes ranging from 10 to 100 mL), a high crossover rate from initial conservative treatment to surgery, and lack of standardized procedures for both surgical intervention and conservative treatment. Early surgery may be only one important therapy for 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 minimally invasive techniques could play a role in the treatment of subsets of ICH patients.

Cardiac Arrest

After 2 seminal studies that showed that hypothermia improves outcome, hypothermia has become a standard of care for the treatment of patients with cardiac arrest due to ventricular fibrillation. It has since been hypothesized that earlier cooling would result in better outcome. In a study by Kim et al., patients with cardiac arrest were randomized to prehospital cooling with infusion of chilled (4°C) saline versus standard of care during a 5-year period. The study included all patients with cardiac arrest regardless of initial rhythm; the goal temperature for cooling was \( \geq34°C \). The primary analysis included 1359 patients. For patients who also received hospital cooling, the administration of cooled saline in the prehospital setting reduced the time to goal temperature by more than an hour (4.2 versus 5.5 hours; \( P<0.001 \)). Prehospital cooling, however, did not decrease mortality or improve neurological outcome at the time of hospital discharge. Furthermore, patients treated with chilled saline in the field were more likely to have a reaerest and evidence pulmonary edema at hospital admission. A separate study casts doubt on the benefit of hypothermia in patients with out-of-hospital cardiac arrest.11 In a randomized controlled study comparing 2 temperature goals, Nielsen et al.\(^\text{11}\) found no decrease in mortality or improvement in neurological outcome in patients randomized to hypothermia (33°C) compared with those where the focus was to avoid fever (36°C). These trials suggest that decreasing the time to achieve hypothermia confers no benefit. Moreover, the value of hypothermia itself is questioned. Additional studies will be needed to determine the true value of hypothermia after cardiac arrest, appropriate temperature targets, duration of therapy, and methods for cooling.

Disclosures

None.

References


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在这一领域内的众多出版物中, 下文讨论的这些似乎与临床实践最为相关。

缺血性卒中

组织型纤溶酶原激活物 (tPA) 静脉溶栓是被证实能改善缺血性卒中结局的唯一疗法。静脉内溶栓治疗的研究表明治疗效果具有时间依赖性; 患者接受 tPA 治疗越早, 获得良好预后的机会越大。1 tPA 使用之前需要进行脑影像学检查会延误治疗的开始时间, 因为这需要转送患者。在院前急性神经科治疗和卒中优化管理 (PHANTOM—S) 队列研究中, Weber 等 2 试图通过在到达医院之前使用 tPA 加快卒中治疗速度。当疑似卒中的患者联系急救医疗系统 (EMS) 时, EMS 会派遣一个配备 CT 的移动卒中急救单元。脑影像检查在现场进行, 从而使 tPA 能在移动卒中急救单元内应用。对卒中急诊移动单元内的患者, 从急救电话到开始应用 tPA 治疗的中位时间是 58 分钟 (5 - 63); 而在历史对照组中是 92 分钟 (79 - 112)。PHANTOM—S 研究是在德国城市完成的一项非随机研究。一项在德国更多乡村地区完成的随机对照研究显示, 与那些在急诊室治疗的患者相比, 在配备 CT 的移动卒中单元内治疗的患者至应用 tPA 治疗的时间也相对缩短。3 这些研究表明, 配备 CT 的移动卒中单元可以缩短到 tPA 应用的时间, 这会转化为显著的临床获益。

高血糖与不良卒中预后有关, 但没有证据证实严格控制血糖可以改善预后。假定积极控制血糖可以减轻梗死扩大, 为了验证这一概念是否正确, 将症状发生后 < 6 小时的颈动脉病变性卒中患者随机分为强化胰岛素治疗组 (N=87) 和标准 (皮下) 胰岛素治疗组 (N=89)。4 在强化胰岛素治疗组, 连续 24 小时输注, 目标血糖 < 7mmol/L (< 126mg/dL)。MR 影像在发病后 < 5 小时 (随机化之前) 和停止治疗后各做一次。尽管强化胰岛素治疗方案改善了血糖控制, 但它却与梗死的扩大有关。5 这些研究表明, 配备 CT 的移动卒中单元可以缩短到 tPA 应用的时间, 这会转化为显著的临床获益。

脑出血

在 INTERACT1 (Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) 预试验之后, 大规模 INTERACT2 研究旨在验证快速降低血压 (随机化分组后 1 小时内目标收缩压 < 140mmHg, 维持 7 天) 6 是否比当前指南建议的治疗 (目标收缩压 < 180mmHg)7 能更好地改善脑出血 (intracerebral hemorrhage, ICH) 患者的预后。患者在症状发生后 < 6 小时接受治疗; 排除标准包括血管结构性出血、昏迷 (中位 Glasgow 昏迷评分, 14)、巨大血肿 (中位体积, 11mL)、预后差以及计划立即手术。纳入了 2794 例可以确定 90 天主要功能结局 (改良 Rankin 评分) 的患者, 入组时平均血压是 179/101mmHg。治疗后 1 和 6 小时收缩压在强化治疗组是 150mmHg 和 139mmHg, 在常规治疗组是 164mmHg 和 153mmHg。主要功能预后 (死亡或严重残疾) 在两组之间没有差异。然而, 对改良 Rankin 评分的次第分析表明, 强化治疗组患者的预后有显著改善, 总体健康状况更好 (health-related quality, EQ-5D 评分; P=0.002)。这一点 INTERACT2 的局限性: 尤其是在急性期降压药物和临床管理都未标准化。正在进行中的脑出血降压治疗 (ATACH II) 试验将提供关于 4.5 小时内静脉应用尼卡地平强化降压治疗的进一步数据。8 尽管 INTERACT2 的主要终点是阴性结果, 但表明了快速降压是安全的, 并且在症状相对较轻和 (或) 出血量较少的患者可能改善功能预后。对自发性 ICH 患者, 降压目标定为收缩压 < 140mmHg 是合理的。

脑叶出血外科手术试验 (Surgical Trial in Lobar Intracerebral Hemorrhage, STICH) II 是一项国际多中心临床研究, 比较了早期手术治疗和保守治疗的疗效。9 研究纳入发病 48 小时内、无脑室出血、表浅脑叶出血 (出血量在 10~100mL) 的清醒患者。共入组 601 例患者随机分配, 手术组 307 例, 保守治疗组 294 例。不良预后 (依据 Glasgow 结局量表) 在早期手术组是 59%, 在初始保守治疗组是 62% (比值比, 0.86; P=0.367)。对开始分至初始保守治疗组的患者, 观察期内, 以窗median}
的转换率以及缺乏标准化的手术治疗和保守治疗有关。对于ICH患者，早期手术可能是仅有的一种重要的治疗方法。正在进行中的CLEAR-IVH研究（Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage, CLEAR-IV）和MISTIE研究（Minimally Invasive Surgery Plus tPA for ICH Evacuation, MISTIE）将证明微创手术是否在ICH患者治疗中发挥一定的作用。

心脏骤停

第二项证实低温疗法能改善预后的开创性研究之后，低温疗法已成为用于治疗室颤颤动所致心脏骤停患者的标准治疗。此后，人们一直假设，降温越早，患者的预后越好。在由Kim等做的为期5年的研究中，不管初始化律如何，纳入所有心脏骤停患者，将患者随机化分到低温组（院前注射4℃冷盐水）与标准治疗组，降温的目标值是≤34℃。初步分析了1359例患者。入院后也接受低温治疗的患者，使院前低温治疗达到目标体温的时间缩短了1小时以上（4.2对5.5小时，P<0.01）。然而，院前低温治疗并没有降低死亡率或改善出院时神经功能预后。此外，现场接受冷盐水治疗的患者在入院时更可能再次发生心脏骤停和明显肺水肿。另一项独立研究对院外心脏骤停患者低温治疗的益处也提出了质疑。

在Nielsen等进行的一项比较2个低温目标的随机对照研究中，比较低温（33℃）患者与重点避免发热（36℃）的患者，结果发现没有降低死亡率或改善神经功能预后。这提示降温到到达低温的温度没有益处。总之，低温治疗的价值值得怀疑。因此，尚需进一步研究来确定心脏骤停后低温治疗的真正价值、合适的低体温目标值、治疗持续时间和降温的方法。

参考文献