Current management of acute ischemic stroke

Part 2: Antithrombotics, neuroprotectives, and stroke units

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ABSTRACT

OBJECTIVE To help family physicians who care for patients with acute stroke or who are involved in planning service delivery or resource allocation to understand recent developments in acute stroke care.

QUALITY OF EVIDENCE A MEDLINE search indicated that most data were derived from well designed, randomized, double-blind, placebo-controlled trials, including all the largest international studies and large systematic reviews.

MAIN MESSAGE Routine anticoagulation is not recommended except for circumstances such as cardioembolic stroke or deep vein thrombosis prophylaxis. Antiplatelet therapy with low-dose acetylsalicylic acid (or another antiplatelet agent if ASA is contraindicated) should be initiated within 48 hours of stroke onset, although benefit is modest. Dedicated care for stroke patients reduces morbidity and mortality and can be cost effective. Recent research into defibrinogenating and neuroprotective agents suggests some benefit, although none are currently licensed for use. Combination therapy might be the answer.

CONCLUSION Management of acute stroke is an emerging discipline; many potential therapies are still experimental.

RÉSUMÉ

OBJECTIF Aider les médecins de famille qui prennent soin de patients victimes d'accidents vasculaires cérébraux (AVC) ou qui planifient la prestation des services ou l'attribution des ressources à comprendre les récents faits nouveaux dans la prise en charge de tels patients.

QUALITÉ DES DONNÉES Une recension dans MEDLINE a permis de cerner que la majorité des données étaient tirées d'études aléatoires contrôlées contre placebo, à double insu et bien conçues, notamment toutes les plus grandes études internationales et les revues systématiques de grande envergure.

PRINCIPAL MESSAGE Il n'est pas recommandé de procéder à une anticoagulothérapie systématique sauf dans des cas comme l'AVC cardio-embolique ou la prophylaxie de la thrombose veineuse profonde. Un traitement antiplaquettaire à l'aide d'acide acétylsalicylique à faible dose (ou d'un autre agent antiplaquettaire si l'AAS est contre-indiquée) devrait être amorcé dans les 48 heures de l'apparition de l'AVC, quoique ses avantages soient modestes. Des services de soins spécialement consacrés aux AVC peuvent réduire la morbidité et la mortalité et peuvent être rentables. Les récentes recherches sur les agents défibrinogénérateurs et neuroprotecteurs font valoir certains bienfaits, mais aucun n'est actuellement homologué. Une polythérapie pourrait se révéler la solution.

CONCLUSION La prise en charge des AVC est une discipline émergeante; de nombreuses thérapies potentielles en sont toujours au stade expérimental.

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CME

Current management of acute ischemic stroke
Part 2

Cerebrovascular disease remains a major cause of morbidity and mortality in North America.[1] Because incidence of stroke rises with age, the magnitude of this problem will likely increase as life expectancies grow longer. Hill and Hachinski[2] have stated, however, that "nihilistic attitudes about stroke treatment are now archaic, because the future holds much promise for stroke patients."

This article reviews some additional aspects of current treatment of acute stroke: anticoagulant and antiplatelet agents, neuroprotective drugs, and specialized care in stroke units. Two important aspects of current stroke treatment, thrombolysis and an organized system of emergency services, were discussed in Part 1 of this series (page 1787).

Family physicians are usually directly involved in treatment of stroke patients, often in conjunction with specialists, but sometimes by themselves. While thrombolysis should be administered only by physicians and in centres with special expertise and training, patients or their families often turn to their family physicians for guidance. Because family physicians also play an advocacy role, understanding recent developments in treatment of acute stroke will allow them to contribute to the debate about service delivery and resource allocation.

Quality of evidence

A MEDLINE search was undertaken using the key words stroke, cerebrovascular accident, antiplatelet, anticoagulant, defibrinogenating agent, neuroprotective, and stroke unit. Most data were derived from randomized, double-blind, placebo-controlled trials with a range of sample sizes; all the largest international studies were included. Large systematic reviews and meta-analyses were also consulted. All these trials are cited frequently in the neurology literature and are considered by experts to be the best evidence to date.

Anticoagulants

Heparin has long been used in treatment of nonhemorrhagic stroke, but little evidence suggests it has any effect on death rates or neurologic outcome.[3,4] Hankey[5] has suggested that many heterogeneous causes of ischemic stroke are unlikely to be influenced by heparin therapy. Although neurologists prescribe heparin for patients with acute ischemic stroke, more than 50%, when surveyed, questioned the efficacy of anticoagulation and cited concerns about safety.[6]

One of the largest ever trials of anticoagulation for acute stroke, the International Stroke Trial (IST), a randomized controlled trial (RCT) of heparin and acetylsalicylic acid, was published in 1997.[7] In this very large study, 19 435 patients were randomized within 48 hours of stroke onset to receive either low- or medium-dose unfractionated heparin, or ASA, or placebo for 14 days. Recurrent strokes and early mortality were both decreased with the lower dose of heparin (5000 U twice daily), the latter because of a reduction in fatal pulmonary embolism.[7] Any benefits of the lower dose were more than offset by an increase in intracranial and extracranial hemorrhage and higher mortality with the medium dose (12 500 U twice daily).[7] Results of this study raised serious concerns about the safety and efficacy of heparin for acute ischemic stroke, but did not lead to universal cessation of heparin therapy.[5]

Gubitz and associates[8] did a systematic review of 21 trials comparing all types of early anticoagulation with placebo. These trials involved more than 23 000 patients, including the 19 000 subjects from the IST,[7] and varied considerably in design and quality. Anticoagulants tested were unfractionated heparin, a variety of low molecular weight heparins (LMWHs) and heparinoids, warfarin, and thrombin inhibitors. Although anticoagulant therapy was associated with fewer recurrent ischemic strokes and pulmonary emboli, no evidence indicated that anticoagulation of any kind reduced the odds of death or dependence (odds ratio [OR] 0.99; 95% confidence interval [CI] 0.94 to 1.05). Their data did not support routine use of any type of anticoagulant therapy for acute ischemic stroke.[8]

Some researchers believe that other forms of anticoagulation, such as LMWHs and heparinoids, are safer and more effective than unfractionated heparin. Certainly, these agents have many theoretical benefits over unfractionated heparin.[9] Several studies examining this issue have been published to date, and more are under way.[10,11]

Counsell and Sandercock[12] have done a systematic review of five trials of early anticoagulation, comparing heparinoids and LMWHs with standard unfractionated heparin. Four of these trials looked at danaparoid, and one examined the LMWH, enoxaparin. A total of 705 subjects were involved. Overall, there was a significant reduction in risk of deep venous thrombosis (DVT) with use of heparinoids and LMWHs,

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but the number of major events, such as pulmonary embolism, intracranial hemorrhage, and death, was too small to provide a reliable estimate of more important benefits and risks.[12]

Hankey[5] has suggested that heparin might be indicated for stroke-in-evolution, vertebrobasilar thrombosis, DVT prophylaxis (at low dose), and cardioembolic infarction.[5] Regarding cardioembolic infarction, the European Atrial Fibrillation Trial (EAFT)[13] showed that, for patients presenting with ischemic stroke and nonrheumatic atrial fibrillation who have a higher risk of death and recurrent stroke, anticoagulation reduced risk of further stroke by 67%.[13] At present, numerous studies are looking at anticoagulation with a variety of different agents for these and other cerebrovascular conditions.

Defibrinogenating agents

Ancrod, a defibrinogenating agent derived from the Malayan pit viper's (*Angkistrodon rhodostoma*) venom, has shown promise for acute stroke treatment in a series of small clinical trials.[4] The Stroke Treatment with Ancrod Trial (STAT), the first large RCT of ancrod for acute ischemic stroke,[14] enrolled 500 patients and randomized them to receive either ancrod (248 patients) or placebo (252 patients). Treatment was initiated within 3 hours of stroke onset and given as a continuous 72-hour infusion, the initial dose based on body weight and baseline plasma fibrinogen levels. Additional 1-hour infusions were given at 96 and 120 hours. The study was designed to keep plasma fibrinogen levels low (approximately 50% of baseline values) for the duration of treatment. Plasma fibrinogen levels were regularly monitored for 3 to 5 days, and dose of the infusion adjusted accordingly. Blood pressure was strictly controlled, and no antithrombotics were administered for the first 24 hours.

The primary efficacy end point was complete recovery at 90 days. This was achieved by more patients in the ancrod group (42.2%) than in the placebo group (34.4%; $P = .04$), and the proportion of severely disabled patients was significantly lower in the ancrod group than in the placebo group.[15] There was a trend toward more symptomatic ICH in the ancrod group (5.2% versus 2.0%; $P = .06$), but the 90-day mortality rate was similar for both groups.[15] The authors concluded that "ancrod [has] a favourable benefit-risk profile for patients with acute ischemic stroke."[15]

Two other "snake-venom therapy" trials are under way and expected to report in 2001. In China, a trial involving 2400 patients is investigating defibrinase, which is derived from *Angkistrodon actus*.[16]

Antiplatelet agents

The role of antiplatelet agents in secondary prevention of stroke is well established.[17] In acute cerebral ischemia, leukocyte-endothelial interaction leads to platelet activation. Some early research suggested a beneficial effect from platelet inhibition during the late (24 to 48 hours) phase of acute cerebral ischemia.[17,18]

The Antiplatelet Trialists' Collaboration, a meta-analysis published in 1994,[18] examined 145 secondary prevention trials in which more than 100 000 patients had been randomized to receive an antiplatelet agent (predominantly ASA with or without dipyridamole or ticlopidine) or placebo. Results indicated that low-dose ASA (75 to 150 mg/d) inhibits platelet cyclooxygenase activity and reduces risk of further strokes and other vascular events by about 22%.[18] This translates into about 40 vascular events avoided per 1000 patients treated.[18] Larger doses of ASA are no more effective but are associated with more side effects.[19]

As discussed above, 19 435 patients in the IST were randomized within 48 hours of stroke onset to receive either ASA (300 mg/d) or placebo.[7] Patients were also randomized to receive either one of two heparin regimens or placebo. Regarding antiplatelet treatment, ASA was found to decrease mortality and recurrent strokes at 14 days, but the decrease was not statistically significant.[7] At 6 months, however, the ASA group was shown to have a significantly reduced risk of death or dependence.[7]

In the Chinese Acute Stroke Trial (CAST), 21 106 patients were randomized within 48 hours of stroke onset to receive either ASA (160 mg/d) or placebo for 4 weeks.[19] Compared with placebo, ASA non-significantly reduced mortality and risk of recurrent ischemic stroke[19] and reduced rate of death or dependence at discharge by about 5%, but slightly increased risk of hemorrhagic stroke.[19]

If the results of these two large trials are combined, a small but clear benefit can be seen with ASA.[17,19] Rate of death or non-fatal recurrent stroke was reduced by 1% among treated patients; rate of death or dependence was decreased by about 1.3%.[20] Both these decreases were statistically significant.

Gubitz et al[21] did a systematic review of the eight major trials of antiplatelet therapy for acute stroke. In their analysis, most data came from the IST and the CAST.[7,19] These authors concluded that antiplatelet therapy with ASA at a dose of 160 to 300 mg/d started within 48 hours of stroke onset reduces risk of early recurrent ischemic stroke and improves long-term outcome.[21]

Antiplatelet treatment slightly but significantly decreased rates of death or dependence at 6 months (OR 0.94; 95% CI 0.91 to 0.98) and also increased the odds of making a complete recovery (OR 1.06; 95% CI 1.01 to 1.11). In absolute terms, 13 more patients were alive and independent at the end of follow up for every 1000 patients treated.[21] Antiplatelet therapy was associated with a small but definite increase in symptomatic ICH (2 cases per 1000 patients treated), but this was more than offset by a reduction of seven recurrent strokes for every 1000 patients treated.[21] Hankey and Warlow,[22] in a study of the evidence and costs of acute stroke treatment, suggest that the number needed to treat with ASA to prevent one death or dependence was 83, and the cost was very low.

Less is known about other antiplatelet agents and their use for acute ischemia.[20] Certainly, in secondary prevention studies, ticlopidine[17] and clopidogrel[23] have been shown to be as good as, or superior to, ASA,[23,24] although ticlopidine might have more adverse effects than either ASA or clopidogrel. Dipyridamole has likewise been evaluated alone and in combination with ASA.[25,26] Alone, dipyridamole is similar in efficacy to ASA, but the combination is likely superior.[26] The role of these antiplatelet agents in acute treatment has not been established, but they could be used if ASA is contraindicated.[18]

Neuroprotectives

To understand how neuroprotective agents can improve outcome from acute cerebral ischemia, physicians must understand the concept of the ischemic penumbra. Although some neurons in the centre of an infarct die within minutes of onset of ischemia, imaging studies show that the surrounding penumbra could take many hours to succumb.[27] Neuroprotective treatment strategies strive to prolong and maintain the viability of ischemic neurons in the penumbral zone until perfusion can be re-established, thus reducing infarct volume.[2]

Ischemia induces release of excitatory amino acid neurotransmitters, such as glutamate, that act at several receptor sites to initiate a complex metabolic cascade that ultimately results in neuron death.[28] The *N*-methyl D-aspartate receptor seems to have a specific, pivotal role.[29] Ischemia also invokes entry of extracellular calcium into neurons via ionotropic receptors, which is extremely damaging to cells and contributes to their death.[28] The ischemia-induced generation of free radicals likewise plays an important role.[30] Neuroprotective agents are targeted at various steps along this ischemic cascade.[17]

Table 1 shows some experimental neuroprotective drugs currently under investigation. Although many of these have shown early promise, none has yet convincingly been shown to benefit human beings.[2] Many phase 2 and 3 trials are currently in design or under way. A very appealing application involves combining neuroprotective therapy to prolong viability of ischemic neurons with thrombolytic therapy to restore perfusion.[2,31]

Table 1. Experimental neuroprotective agents

ION CHANNEL BLOCKERS
Nimodipine
Lifarizine*
GLUTAMATE RECEPTOR BLOCKERS
Aptiganel*
Magnesium salts
GLUTAMATE RELEASE INHIBITORS
Lubeluzole*
Fosphenytoin
***N*-METHYL D-ASPARTATE ANTAGONISTS**
Lifarizine*
Aptiganel*
FREE RADICAL SCAVENGERS
Tirilizad mesylate
Superoxide dismutase
NITRIC OXIDE PATHWAY MODULATORS
Lubeluzole*
OTHERS
Citicholine
Clomethiazole
Nalmefene

**Might have several mechanisms of action.*

Where thrombolytic therapy is contraindicated, neuroprotection alone might provide some benefit. As well, because there are numerous steps along the ischemic metabolic cascade and a variety of drugs with various actions, a cocktail involving several neuroprotective agents might yet prove beneficial.[32]

Stroke units

Overwhelming evidence indicates that dedicated care for stroke victims in specialized stroke units reduces disability and mortality.[33,34] The Stroke Unit Trialists' Collaboration has carried out a systematic review of the 19 major randomized trials (involving 3249 patients) of stroke unit care. They found that such care was associated with a long-term reduction in death and dependence.[33] The OR for death was 0.83 (95% CI 0.69 to 0.98; $P < .05$); the OR for the combined outcome

of death or dependence was 0.69 (95% CI 0.59 to 0.82; $P < .0001$).[33] The number needed to treat (NNT) to prevent one patient from requiring long-term institutional care was 8 to 10, while the NNT for one patient to regain independence was 10 to 25.[33]

Although evidence is limited, it suggests that organized care in a stroke unit is no more expensive than conventional care on a general medical ward.[22] Length of stay in hospital or in an institution was reduced by 8%.[33] Because stroke-unit care has a large beneficial absolute treatment effect and is probably appropriate for most stroke victims, it is likely to be highly cost effective.[22]

While it is clear that stroke-unit care is effective both clinically and economically, it is not clear what factors lead to the reduction in morbidity and mortality seen with dedicated stroke care.[2] Stroke units provide many apparently simple interventions, such as blood pressure control, maintenance of euglycemia, prevention of aspiration, and DVT prophylaxis.[2,34] Recent data confirm the high incidence of serious medical complications among stroke patients,[35] and vigilance with early attention to these complications, if they develop, might enhance outcome.[33] Early mobilization might also promote recovery, prevent complications, and allow earlier discharge.[2,33] The important contribution of early and coordinated rehabilitation was found to be a key component of successful stroke units[33,36] and cannot be overemphasized.

A stroke team formed through the collaboration of various specialists and incorporating the characteristics of effective stroke units[36] could give patients dedicated treatment on any appropriate hospital ward.[28]

Conclusion

Despite a long history of use for nonhemorrhagic stroke, routine anticoagulation is not indicated for acute stroke patients no matter which agent is used. Although LMWHs might offer some theoretical advantages over unfractionated heparin, they have not been proven more effective. Anticoagulation might be indicated for stroke-in-evolution, vertebrobasilar thrombosis, and, in a low dose, for DVT prophylaxis, but there is no proven clear-cut benefit. Anticoagulation is indicated for acute cardioembolic stroke in patients with atrial fibrillation.

Initiation of antiplatelet therapy with low-dose ASA is indicated within 48 hours of stroke onset. Although its benefit is modest, it does reduce risk of recurrence and might improve outcome. Other antiplatelet agents may be used if ASA is contraindicated, but no direct evidence suggests they are beneficial nor superior.

Dedicated care in specialized stroke units reduces morbidity and mortality and can be cost effective. Alternatively, a stroke team might be able to provide similarly effective treatment on any appropriate hospital ward. Early rehabilitation is the key.

As Roberts and Hughes[29] have stated, "… active management of stroke is an *emerging* discipline with many potential therapies still at an *experimental* stage." There does, indeed, seem to be cause for enthusiasm and optimism.

Editor's key points

- Following acute ischemic stroke, the most effective way to increase patients' chances of returning to independent living is to admit them to a stroke unit.
- Starting low-dose acetylsalicylic acid (or another antiplatelet agent if ASA is contraindicated) within 48 hours of stroke has modest benefits.
- Anticoagulation with heparin is useful only for preventing deep vein thrombosis and for atrial fibrillation.
- Current research into defibrinogenating agents, such as snake venom and many neuroprotective medications, suggests benefit, but these therapies are still experimental.

Points de repère du rédacteur

- À la suite d'un accident ischémique cérébral aigu, le moyen le plus efficace d'augmenter les chances du patient de recouvrer son autonomie est de l'admettre dans une unité spécialisée en AVC.
- L'amorce d'une thérapie à faible dose d'acide acétylsalicylique (ou d'un autre agent antiplaquettaire si l'AAS est contre-indiquée) dans les 48 heures suivant l'AVC présente de modestes avantages.
- L'anticoagulation avec l'héparine n'est utile que pour prévenir une thrombose veineuse profonde et en cas de fibrillation auriculaire.
- Les recherches actuelles sur les agents défibrinogénérateurs, comme le venin de serpent et plusieurs médicaments neuroprotecteurs, font valoir certains bienfaits, mais elles n'en sont encore qu'au stade expérimental.

Competing interests
None declared

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