Controversies in Stroke

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Steroids May Have a Role in Stroke Therapy

John W. Norris, MD

Few therapeutic responses are more dramatic than the response to corticosteroids administered overnight to a drowsy and hemiplegic patient with a cerebral tumor, who next morning is alert with minimal neurological disability, even though this effect may be short lived. Unfortunately, no such dramatic response is seen in patients with ischemic or hemorrhagic stroke; but does this mean that such therapy is totally ineffective? The categorization of cerebral edema by Klatzo and Seitelberger into “cytotoxic” and “vasogenic” holds the key to this therapeutic response.

Cytotoxic, or “intracellular,” edema represents the earliest response to cerebral damage, and whether ischemic or traumatic, is due to the breakdown of cellular ionic pumps causing ingress of water into the cell, and confined within the cellular membrane. The clinical effects and response to corticosteroids of this immediate type of edema is uncertain. Vasogenic edema, occurring hours later, is due to damage to the blood-brain barrier, which becomes “leaky,” allowing extravasation of water, electrolytes, and soon protein into the parenchyma. This produces clinically significant brain swelling, resulting in distortion and herniation of brain and causing neurological disability and death. In brain tumors, the normally tight vascular junctions are pathologically separated, and cellular physiology (such as pinocytosis) is otherwise disturbed, resulting in severe vasogenic edema, which is highly responsive to corticosteroids. This fundamental difference in pathophysiology between the 2 types of lesions may explain the apparent difference in their initial therapeutic response.

There is overwhelming evidence experimentally in a variety of mammalian models that corticosteroids effectively reduce ischemic cerebral edema, both focal and generalized, although the credibility gap needed to extrapolate to the human brain, as always, remains uncertain. In a rather contrived but nevertheless convincing series of experiments, de Courten-Myers et al., using hyperglycemic cats, occluded the middle cerebral arteries for 4 hours, administering high-dose corticosteroids 30 minutes after occlusion. Compared with untreated controls, there was a highly significant, 6-fold difference in the size of the resulting infarcts in favor of the treated group. Paradoxically, there was no significant difference in the acute death rate between the 2 groups of animals, but whether this represents the difference between the sensitivity of response to the drug in cytotoxic versus vasogenic edema must remain speculative. Also, there are other unexplored effects of corticosteroids on the brain, such as the unanticipated but significantly increased cerebral blood flow in the treated group of animals. Effective reduction of cerebral edema after corticosteroids has also been documented in animal models of global ischemia.

Hemorrhagic stroke, in both clinical and experimental trials, has been relatively neglected, probably because of a sense of therapeutic nihilism, but there is a rationale for corticosteroid therapy in the reduction of perihematomal edema. Using a pig model, Wagner et al demonstrated that serum proteins accumulated in the white matter around hematoma (produced by injecting autologous blood into the frontal lobe), resulting in rapid and prolonged cerebral edema. Similarly, CT brain scanning of patients with spontaneous intracerebral hemorrhage showed that the volume of perihematomal edema increased by 75% in the first 24 hours after the event and so should be susceptible to edema-reducing drugs such as corticosteroids.

Early reports of the beneficial effects corticosteroid therapy in inflammatory and neoplastic brain lesions made it a victim of its own success in stroke patients, since a flurry of early clinical trials in anticipation of similar benefits were conducted before enough was known about either the natural history of stroke or correct methodology of clinical trials. Most trials that were conducted were too little or too late, resulting in the premature abandonment of this potential therapeutic avenue. In a recent Cochrane Review, only 7 of 22 published trials of corticosteroids in stroke were acceptable for further analysis, and these comprised woefully inadequate numbers of patients (only 453 in total) with no uniformity of evaluation or assessment, and totally disparate conclusions. No trials have been conducted since 1986. These generally negative results did not deter physicians from the United States or China from administering corticosteroids in stroke patients, however, and 20% of physicians surveyed in both countries reported that they still used them routinely, at least in ischemic stroke.

The Cochrane reviewers concluded that with the available data, they were reluctant to advocate a large-scale therapeutic trial, but that corticosteroid therapy could be factored in as an additional arm of a large trial of a more promising drug. Unfortunately, so far significantly more than 100 neuroprotective trials in acute stroke have proven negative, and it is...
Steroids Have No Role in Stroke Therapy

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Steroids are considered as a group of the magic drugs and have been widely used in neurology for more than 40 years. Theoretically, steroids are immunosuppressive agents, lessen the damaging effects of vasogenic cerebral edema, decrease intracranial pressure, and strengthen the blood-brain barrier. However, these possible benefits have to be weighed against potentially serious steroid-related side effects such as immunosuppression and infection, diabetic exacerbation, gastrointestinal hemorrhage, and compromised wound healing.

The place of steroids in the management of stroke is still controversial. As stroke is a heterogeneous condition, it is therefore unlikely that a single agent would be beneficial in any treatment plan. Perhaps the only general agreement on the use of steroids in stroke is where vasculitis is suspected or proven. As stroke is a heterogeneous condition, it is unlikely that industry would welcome such a potential confounding factor to a therapeutic trial of their own drug already costing tens of millions of dollars.

A corticosteroid trial in stroke, with sufficient numbers of patients and rigorous methodology, will therefore have to remain a Cinderella until sufficient academic interest and funding become available.

References

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Steroids for Stroke: Another Potential Therapy Discarded Prematurely?

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Why do we discard potentially promising therapies so easily? First, the perception that the evidence has been adequately assessed becomes ingrained in the thought processes of everyday practitioners. Second, there is no commercial imperative to drive new trials of therapy. In virtually any modern review of acute stroke therapy, a statement is included that corticosteroids are disproven. However, when the evidence for the Cochrane Review of steroids for acute ischemic stroke is examined in more detail, the data seem to be disturbingly sparse. For example, the Cochrane Review of steroids for acute ischemic stroke could identify only 7 trials that met their criteria for evaluation, and these involved only 453 patients.1 Furthermore, the last of these trials was published in 1986, by Norris and Hachinski.2 In intracerebral hemorrhage (ICH), there appear to be only 3 randomized control trials targeting ICH alone, involving only 159 patients.3,4 However, it should be noted that Poungvarin, one of our protagonists, performed the most rigorous and most often cited study of steroids in ICH in 1987.5 To date, the amount of evidence is minimal and there have been no recent large...
trials. Methodological problems also include long time windows, uncertainty about dose, protracted steroid treatment, and lack of rigorous monitoring and correction of potential steroid side effects, particularly hyperglycemia.

The theoretical constructs involved here are important, as outlined by Norris. He nicely draws attention to the important differences between vasogenic and cytotoxic edema and their temporal relationships. Practicing clinicians would be well aware that the edema surrounding ICH, commonly seen on CT and MR images, includes vasogenic as well as cytotoxic components. In ICH, the perihematoma edema volume substantially increases in the first 24 hours after onset and is independently predictive of functional outcome.\(^6\) Hence, it would seem more logical to study the effects of steroids in cases of hemorrhage rather than infarction, where it is generally considered that cytotoxic edema predominates.

Modern trial principles for any re-evaluation of steroids in stroke would require administration of therapy during an earlier time window, use of high-dose intravenous steroids (such as methylprednisolone), a shorter duration of therapy to avoid potential side effects, and adequate sample size. Adverse effects of steroid therapy, such as hyperglycemia, infections, and gastrointestinal hemorrhage, have offset any trend to improvement in ICH in previous trials.\(^4\) These would need to be considered in trial design. For example, with the modern understanding of the adverse effects of hyperglycemia in acute stroke, rigorous glycemic monitoring and insulin therapy would be required. Both of our protagonists have published widely quoted negative studies concerning steroids in stroke.\(^2,4\) Norris points out that steroid use remains prevalent, nonetheless, in many countries. This is an ideal scenario for a high-quality investigator-driven trial to be generated. Clearly, this has no commercial attraction, as is the case with many potentially promising but prematurely discarded therapies. We will watch with interest.

**References**


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