Heparin use in acute ischaemic stroke: does evidence change practice?

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Introduction
There has been much discussion in recent years about the importance of evidence-based medicine and, although the discipline has received broad acceptance, it is not without its critics. An important question that has received relatively little attention is: what is the evidence that evidence-based medicine has had any effect on practice? In this article, I shall try to answer this question with respect to the use of heparin in the management of acute ischaemic stroke. I will not consider the unusual instances of extra-cranial arterial dissection, cerebral venous thrombosis and crescendo transient ischaemic attacks, but will instead focus on the more common causes of acute ischaemic stroke for which heparin anticoagulation is still frequently used.

Acute ischaemic stroke is a common problem that carries a significant risk of death and disability. There are approximately 600,000 new cases diagnosed each year in the USA with about 150,000 deaths and a further 300,000 survivors left with substantial disability. The use of heparin in the management of acute ischaemic stroke has been the subject of many studies, including a number of randomized controlled trials. Low-molecular-weight heparin, administered subcutaneously, was used in most studies, although a few have examined the use of intravenous unfractionated heparin. For the most part, these studies (Table 1) have shown no benefit from heparin, with the small decrease in the risk of stroke progression or recurrence being offset by an increase in the risk of hemorrhagic complications. What has been the impact of these results? Has there been a decline in the usage of heparin since publication of these results? If not, why not? These are the questions that are considered in this paper.

Has the evidence had any effect on practice?
There are limited data upon which to base an answer to this question. A few studies have examined the prescribing behaviour of neurologists, with one of these conducted prior to publication of most of the studies cited in Table 1, and one published subsequently. Each had a similar design, in that a sample of American neurologists was asked to complete a questionnaire in which a series of case vignettes were presented. The vignettes described instances of a stroke-in-evolution, cardio-embolic stroke, stroke in the carotid and vertebro-basilar circulations, respectively, and a transient ischaemic attack. Neurologists were asked to indicate whether they would treat the patient described in the vignette, with heparin. Comparison of the results of these two studies (Table 2) suggests that there has been a change in neurologists’ pattern of heparin use. In the second survey, fewer neurologists indicated that they would use heparin to treat transient ischaemic attack, stroke-in-evolution and ischaemic stroke in either the...
<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Study population</th>
<th>Study endpoint</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CESG (1983)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>UFIVH</td>
<td>All patients with cardioembolic stroke within 48 h of onset*</td>
<td>Early recurrent cerebral embolism</td>
<td>n = 45. Trend towards reduction in study endpoint amongst those anticoagulated</td>
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<tr>
<td>Duke (1986)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>UFIVH</td>
<td>Partial stable stroke within 48 h of onset</td>
<td>Change in neurological status, number of patients with stroke progression and functional outcome at 7 days, 3 months &amp; 1 year</td>
<td>n = 225. No differences observed between endpoints amongst the two treatment groups</td>
</tr>
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<td>FISS (1995)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>LMWH (fraxiparin)</td>
<td>Acute ischaemic stroke within 48 h of onset*</td>
<td>Death or dependency at 6 months</td>
<td>n = 308. Favourable effect of heparin</td>
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<td>IST (1997)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>UFSQH</td>
<td>Acute ischaemic stroke within 24 h of onset*</td>
<td>Death at day 14, death or dependency at 6 months</td>
<td>Non-blinded; aPTT not monitored; no benefit from heparin</td>
</tr>
<tr>
<td>TOAST (1998)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>LMWH (danaproid)</td>
<td>Acute ischaemic stroke within 24 h of onset*</td>
<td>Glasgow outcome scale &amp; Barthel index</td>
<td>n = 281. No difference in treatment groups except for ‘large artery stroke’ subgroup</td>
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<tr>
<td>TAIST (1998)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>LMWH (tinzaparin)</td>
<td>Acute ischaemic stroke within 48 h of onset</td>
<td>Modified Rankin score at 6 months</td>
<td>n = 1486 (no placebo group). No differences between treatment groups</td>
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<td>FISS-Bis (1998)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>LMWH (fraxiparin)</td>
<td>Acute ischaemic stroke*</td>
<td>Mortality, neurological impairment, Barthel index and Rankin score</td>
<td>n = 767. No differences between treatment groups</td>
</tr>
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<td>TOPAS (2001)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>LMWH (certoparin)</td>
<td>Acute ischaemic stroke</td>
<td>Barthel index</td>
<td>n = 404; no placebo group. No difference between treatment groups</td>
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<tr>
<td>HAEST (2000)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>LMWH (dalteparin)</td>
<td>All patients with cardioembolic stroke within 30 h of onset*</td>
<td>Recurrent ischaemic stroke within 14 days, functional outcome, death</td>
<td>n = 449. No differences between two treatment groups</td>
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CESG, cardioembolism study group; UFIVH, unfractionated intravenous heparin; UFSQH, unfractionated subcutaneous heparin; LMWH, low-molecular-weight heparin (heparinoid); FISS, Fraxiparine in Ischaemic Stroke Study; IST, International Stroke Trial; HAEST, Heparin in Acute Embolic Stroke Trial; TOAST, Trial of ORG10172 in Acute Ischemic Stroke; TAIST, Tinzaparin in Acute Ischaemic Stroke Trial; TOPAS, Treatment of Patients with Acute ischemic Stroke. *Included patients with cardioembolic stroke.
vertebrobasilar or carotid circulations. The usage of heparin in the treatment of cardioembolic stroke remained in excess of 90% and was essentially unchanged between the two studies.

There are many reasons to be cautious in accepting these data. They indicate the responses provided by neurologists in answering a questionnaire, and it is unclear how accurate a representation this provides of their actual practice. Furthermore, the response rate, particularly for the second questionnaire in 2001, was only 40%, so significant selection bias may have been introduced. Nevertheless, these data do provide some insight into the opinions expressed by practicing neurologists who regularly manage patients with acute ischaemic stroke.

Why does the practice of heparin anticoagulation for acute ischaemic stroke persist?

There are no data available to answer this question, but in the discussion that follows I speculate on possible reasons, drawing from clinical experience, interaction with colleagues and a careful reading of the literature.

Are neurologists aware of the evidence?

One possible explanation for why neurologists persist in the use of heparin might be that they are not aware of the published data. The results of the trials that have examined the use of heparin in acute ischaemic stroke have been published, for the most part, in main stream journals including The Lancet, the New England Journal of Medicine and the Journal of the American Medical Association. Furthermore, the publication of these trials has been accompanied and followed by editorials, reviews and meta-analyses. It is difficult to believe that neurologists are not aware of the publication of these studies. It may be, however, that many neurologists have not read this literature as carefully as they should. Most of the studies examining the usefulness of heparin in acute ischaemic stroke have used fractionated low-molecular-weight heparin (heparinoids) administered subcutaneously in a standard dose. The data examining the use of intravenous unfractionated heparin in a dose-adjusted fashion, however, is more scanty. Although neither of these studies showed an unequivocal benefit from heparin, it is true that most of the literature on heparin use in acute ischaemic stroke has not examined the use of heparin in the fashion most commonly used by neurologists (dose-adjusted intravenous unfractionated heparin). To the extent that there is confusion over this issue, it may be true that many neurologists are not aware of the evidence.

Do neurologists disagree about the interpretation of the evidence?

The titles ‘Resolved: Heparin may be useful in selected patients with brain ischemia’ and ‘Full heparin anticoagulation should not be used in acute ischemic stroke’ appeared in a recent issue of the journal Stroke as part of the ‘Controversies in Stroke’ column. While the authors of these two articles concur that heparin should not be used indiscriminately in all patients with acute ischaemic stroke, the one author concludes ‘Until more definitive trials are performed, I use heparins in patients with: large artery occlusions and severe stenosis; cardioembolic stroke with high acute recurrence risk; dural sinus and cerebral venous thrombosis’. The author of the second article states ‘I believe the available data would not be sufficient to support a product license for [intravenous unfractionated heparin] in acute ischaemic stroke...I would be very interested to know how, given the lack of evidence, the clinicians who use IV heparin in acute stroke justify this unproven treatment to their patients’. These and other editorials and opinion pieces suggest that there remains significant disagreement about what the evidence actually shows.

One of the most contentious issues is the use of heparin in patients with atrial fibrillation or cardioembolic embolism of another aetiology. The increased early risk of recurrent ischaemic stroke for patients...
with cardioembolic stroke (4.5–8%) compared to stroke patients of any aetiology (~2.2%) has been used to justify early anticoagulation with heparin. Most of the heparin trials, however, included patients with cardioembolic stroke\(^{4,7-9,11,12}\) and one (HAEST) was entirely devoted to studying this population of patients\(^{11}\) (Table 1). Therefore, notwithstanding the increased risk of stroke recurrence amongst patients with cardioembolic stroke, the available data still do not support the use of heparin anticoagulation.

One, perhaps legitimate, disagreement among neurologists relates to the use of intravenous dose-adjusted unfractionated heparin rather than subcutaneous low-molecular-weight heparin. The proponents of heparin use point to the fact that most studies have examined the use of the latter rather than the former and hence bear little relevance to their advocacy of intravenous unfractionated heparin. This area of disagreement has spawned the European RAPID (Rapid Anticoagulation Prevents Ischaemic Damage) Trial that aims to randomize 1400 patients with acute ischaemic stroke to intravenous weight-adjusted unfractionated heparin or aspirin within 12 h of the onset of symptoms. Hopefully, the results of this study will settle this area of dispute.

### Does heparin use persist because old habits are hard to break?

The early evidence, albeit of limited quality, was taken to indicate that heparin was effective in the treatment of acute ischaemic stroke due to cardioembolic disease.\(^{12}\) In view of the general therapeutic nihilism of neurologists 20 years ago when these results were first published, it is perhaps not surprising that neurologists enthusiastically endorsed the use of an active intervention that was purported to save lives. Having recommended the use of heparin for many years, it may be difficult for neurologists now to accept that the initial practice was wrong, as this requires an admission that the practice was mistaken, as well as the abandonment of an active treatment that was once held in such high regard. To some extent, pride may inhibit such an admission of fault.

### Does heparin use persist because of the expectation that it should work?

The expectation that heparin should be effective in the treatment of acute ischaemic stroke derives in part from its successful use in the treatment of patients with myocardial infarction. Heparin has been shown to reduce morbidity and mortality in patients with acute coronary ischemia. Based on the anticipated similarities between the pathophysiology of acute brain and acute myocardial ischemia, neurologists had anticipated that heparin should also be effective when used in patients with acute ischaemic stroke. The high expectation may have clouded neurologists’ interpretation of the evidence relevant to heparin use in ischaemic stroke.

### Does personal experience trump the evidence?

Neurologists, like all physicians, learn from their experience. There may be a tendency to recall the most recent experience, and to base practice on the outcome of this experience. Regrettably, such clinical experience usually only amounts to anecdote, and since it is uncontrolled, it is unreliable in extrapolating to how patients with similar problems should be managed in the future. Furthermore, such anecdotal experience is highly susceptible to recollection bias, with those favouring the use of heparin likely to recall only patients in whom heparin appeared to be successful.

### Do medico-legal considerations influence neurologists’ practice?

The one study that surveyed neurologists’ opinions about the use of heparin in various stroke scenarios compared the responses of a sample of neurologists in the US with a sample from Canada.\(^{2}\) While both groups agreed on the use of heparin for patients with atrial fibrillation and/or cardioembolic stroke, heparin was endorsed much less frequently by Canadian neurologists. The authors’ survey included a question about the impact of medico-legal concerns, and more US neurologists indicated that such concerns impacted their decision at least sometimes (33% US neurologists vs. 10% Canadian neurologists).\(^{2}\)

### Are there psychological factors that contribute to the persistent use of heparin?

Covert peer pressure and the tendency for trainees to adopt the prescribing habits of their teachers may play an important role in shaping neurologists’
practices. It may be, therefore, that the more common usage of heparin amongst US neurologists is self-perpetuating. If neurologists in training observe their teachers administering heparin to patients with acute ischaemic stroke, they may be inclined to initiate this practice themselves. Other psychological factors may also play a role. There may be an inclination to adopt the ‘active’ practice of administering heparin rather than the ‘passive’ practice of not using heparin to anticoagulate patients with acute ischaemic stroke. The motivation for such a tendency likely results from the desire of the clinician actively to do something for the patient under her care. Patients and their families may then feel that the neurologist at least did what she could. This perception may be regarded as more favourable than that of the patient who feels that the neurologist didn’t do anything for him at the time of his stroke.

Conclusion

The answer to the question of whether the evidence from the many trials of heparin in acute ischaemic stroke has had any effect on practice seems to be mixed. Since the publication of a series of randomized controlled trials indicating the absence of benefit from heparin anticoagulation, there has been some change in practice, with a decline in heparin use for the management of non-cardioembolic stroke, but the overwhelming (and unchanged) majority of neurologists persist in their use of heparin for cardioembolic stroke, and a significant minority continue to use heparin for both anterior and posterior circulation stroke as well as transient ischaemic attacks and stroke-in-evolution. These practices would seem to run counter to the available evidence.

Although, as I have suggested, there are many potential reasons for the persistence of this practice, it is clear that neurologists have not yet reached agreement that adequate evidence exists to show that heparin should not be used. That is to say, many neurologists would argue that there remains an absence of evidence rather than sufficient evidence that argues against the use of heparin for acute ischaemic stroke. This disagreement is particularly evident in the debate over the use of intravenous dose-adjusted unfractionated heparin rather than subcutaneous low-molecular-weight heparin. It seems unlikely, however, that this difference of opinion entirely accounts for the persistent use of heparin by US neurologists in the management of patients with acute ischaemic stroke. I have suggested that a variety of other factors may play a role including reliance on personal anecdotal experience rather than evidence, the difficulties relating to admission that previous practice was flawed, an inertia that impedes a change in prescribing practice, the unwavering perception that heparin should work, the psychological need to actively treat rather than to passively observe, as well as medico-legal concerns. The evidence seems to suggest that evidence-based medicine has had some impact on neurologists’ use of heparin for the management of acute ischaemic stroke, but that the practice persists for a complex variety of reasons.

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References


