Herpes zoster: epidemiological links with stroke and myocardial infarction

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ABSTRACT

Routine data from electronic health records (EHRs) provide insights into links between herpes zoster (HZ) and cardiovascular complications such as stroke or myocardial infarction (MI) in different populations worldwide. Evidence from large EHR studies using both self-controlled case series and traditional cohort designs suggests that there is a transient increase in the risk of stroke after HZ, which gradually resolves over 6 to 12 months. In these studies, herpes zoster ophthalmicus was associated with a higher risk of stroke than HZ at other sites. A larger effect size was seen in people aged under 40 years. Existing studies also suggest that HZ may have a triggering effect on MI, although fewer studies examine this outcome. Further evidence is needed on the effectiveness and cost-effectiveness of vaccine and antiviral drugs to reduce cardiovascular complications after HZ, in studies which are designed to minimise selection biases and confounding by indication.

Introduction

Acute infections, such as influenza, can trigger cardiovascular events including stroke and myocardial infarction (MI)[1,2]. Interest is growing in the effect of persistent reactivating viruses such as varicella zoster virus (VZV) on the pathogenesis of cardiovascular diseases, which are the leading global cause of death. There are biologically plausible mechanisms through which VZV could trigger acute vascular events: inflammatory responses following reactivation of VZV from latency to cause herpes zoster (HZ) may lead to endothelial dysfunction and development of a hyper-coagulable state[3]. Pathological vascular remodelling associated with arterial VZV infection (VZV vasculopathy) may also contribute to vascular risk[4]. As the population ages, the burden of disease due to stroke, including disability, illness and premature death, is projected to double worldwide by 2030[5]. Understanding the current evidence and its limitations is crucial to inform vaccination and treatment strategies to minimise vascular complications of VZV.

Evidence for association between HZ and vascular complications

Historically, the ability to investigate relatively rare complications of infections was hampered by lack of power due to small sample sizes. Now, in the era of "big data", with routinely collected electronic health records (EHRs) available for large numbers of patients with clinically-diagnosed HZ infections, vascular complications can be investigated in different population subgroups with increasing precision. There remain, however, methodological difficulties with interpreting data robustly from studies with different designs, exposure and outcome definitions, populations and settings. In the last year, several systematic reviews synthesized evidence of the relationship between HZ and stroke from cohort and self-controlled case series studies[6–11]. Although the pooled effect estimates presented in these reviews vary due to differing methods and inclusion criteria, the combined evidence suggests the following:

1) HZ can trigger stroke.

There is a transient increase in the risk of stroke after HZ, which is highest in the earliest time period after HZ diagnosis – adjusted incidence ratio (IR) for stroke 2.37 (95% CI 2.17-2.59) up to one week after HZ[12] – and gradually diminishes to baseline by around six to twelve months. At four weeks. data from three powerful self-controlled case series studies using primary care EHRs from the US, UK and Germany, show a pooled IR for stroke of 1.55 (95% C.I. 1.46-1.65)[12–14]. These studies have the major benefit of implicitly controlling for fixed between-person confounding effects[15]. The findings are corroborated by several prospective cohort studies using data from Asian, European and US populations, which show a similar gradient of stroke risk up to one year[16–21]. Evidence for any longer-term effect of HZ on vascular risk is mixed, with marked heterogeneity between studies. A meta-analysis of four cohort studies using random effects found no association between HZ and stroke after one year: pooled OR 1.20 (95% CI 0.82-1.75)[11].

2) Herpes zoster ophthalmicus (HZO) leads to a higher risk of stroke than HZ at other sites.

Point estimates for the effect of HZO on stroke are generally higher than those for HZ at other or unspecified sites. HZO refers to reactivation of VZV in the first division of the trigeminal nerve, and it has been proposed that the proximity of the trigeminal ganglion to cerebral arteries may increase these patients' susceptibility to large vessel stroke.[11] However, many EHR studies do not specify zoster site, which is likely to lead to underestimation of effect because some HZ at unclassified sites could actually be HZO. The stronger effect for HZO was noted in two self-controlled case series studies which stratified by HZ site[12,13] as well as two Asian cohort studies[20,21]. A further study found no effect of HZ site on long-term stroke risk, although few participants had HZO records[22].

3) Stroke risk may be highest for younger people with HZ

Intriguing evidence suggests a more marked effect in younger people. Point estimates for the effect of HZ on stroke are highest for younger people, aged less than 40 years, although the relatively small numbers of strokes in this age group mean that confidence intervals tend to overlap with those for

older ages. Of five cohort studies which stratified by age, four found a greater effect in younger age groups[16,17,22,23] and one study showed no difference in effect size by age[20].

4) HZ can trigger myocardial infarction (MI)

One self-controlled case series study using US Medicare data[12] showed a similar though smaller transient triggering effect of HZ on MI – IR 1.68 (95% CI 1.47 – 1.92) – for week one after HZ. An elevated risk of acute coronary syndrome (ACS) or MI up to 3 months after HZ was also suggested by combined results from two prospective population cohort studies from the US[18] and Taiwan[24]: pooled OR 1.34 (95% 0.98 to 1.82)[11], although this just failed to reach statistical significance in a random effects model. The Taiwanese study also showed a small increase in ACS risk associated with HZ in follow up to 12 years (HR 1.10 (95% CI 1.02 to 1.19)[24], which was mirrored in a cohort using UK primary care data with follow up to 24 years[22].

Table 1

Effect of HZ prevention on vascular complications

It seems plausible that reducing HZ incidence and severity through vaccination is likely to result in fewer vascular complications. A single dose of the live attenuated zoster vaccine (Zostavax) reduces herpes zoster incidence by around 50%.[25] However, at present evidence of direct cardiovascular benefit from the live attenuated zoster vaccine is lacking: in the Shingles Prevention Study, rates of serious adverse events including MI and stroke, were the same in recipients of vaccine and placebo but follow up was short (to 42 days) and the trial was not powered for these endpoints[25]. Observational safety studies have also shown no effect of Zostavax on stroke risk in follow up to 5-6 weeks[26,27], although longer-term follow up is needed to assess fully the vaccine's effectiveness against vascular outcomes. The recent development of the highly efficacious subunit vaccine HZ/su (Shingrix), which reduces HZ incidence by 90% after two doses in older adults[28] has potential for major impact on VZV disease burden, including vascular complications, in settings achieving good

vaccine uptake. A recent modelling study based on RCT data showed that Shingrix, at a price of $280 for two doses, was more cost effective than Zostavax (current price $213 per dose).[29]

Effect of HZ treatment on vascular complications

It remains uncertain whether antiviral agents used to treat HZ alter the risk of vascular events: results from one cohort study[19] and one self-controlled case series study[13] suggest that patients receiving antivirals may have a lower stroke risk than patients not taking antivirals, especially earlier after HZ diagnosis. Another cohort study, however, found no difference in stroke risk at one year between those who did and did not receive antivirals for HZO[21], although data on timing and duration of treatment were unavailable in this study and it was difficult to exclude confounding by indication – the situation in which patients who were more unwell and had a higher risk of vascular complications preferentially received antiviral treatment.

Conclusions

In future, our ability to prevent HZ-induced vascular events will depend upon improving understanding of the nature of risk including any effects of sub-clinical VZV reactivation or long-term effects. Large-scale population-based studies to identify the characteristics of affected patients will help to guide intervention targeting. Adequately powered studies of HZ prevention and treatment strategies against specific vascular endpoints are needed, which are carefully designed to avoid selection biases and confounding by indication. As the evidence base develops, it will be important to (re-)assess the cost effectiveness of policy options such as introducing universal varicella vaccination in countries where it is not routine, for example in Northern Europe, or expanding recommendations for zoster vaccination to include younger age groups at high cardiovascular risk.

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Conflict of interest

None declared.

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