Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 14, ISSUE 10, 2023

Original Research

A clinical study of the patients suffering from Herpes Zoster (Shingles) in correlation with cardiovascular diseases

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Abstract:

Background: The basis for increased cardiovascular events following acute infection is hypothesized to be endothelial dysfunction, characterized by atheromatous plaque rupture and the development of a prothrombotic environment . As acute cardiovascular diseases (CVDs), specifically ischemic stroke and MI, are major causes of morbidity and mortality in the India and worldwide, understanding the basis for acute cardiovascular events and any potential for prevention becomes increasingly important.

Aims and Objectives: To analyze the patients suffering from Herpes Zoster (Shingles) in correlation with cardiovascular diseases.

Materials and Methods: Retrospective study was performed in our private clinics as well as in the department of Dermatology, General Medicine, Cardiology and Neuro-medicine, Santiniketan Medical College and Hospital, Bolpur, Birbhum, West Bengal, India. Sample subjects were 200, distributed in 2 separate group, Non HZ group and HZ group, 100 subjects in each group.

Results and Observations: Overall, 200 subjects were diagnosed with HZ during the study period, 200 patients were included in this study (100 patients per group). The average age at zoster diagnosis was 45.7 (±18.0) years. Of these patients, 33.8 were male, 18% had diabetes mellitus, and 30.5% had hypertension as underlying diagnoses. The follow-up period did not differ significantly between the study groups, with a minimum of 0 and a maximum of 5 years, and a mean follow-up interval of 1.5 years. Cumulative MACCE survival at the end of the follow-up period was 54% in the HZ group as compared to 74% in the non-HZ group ($P<0.001$)

Conclusion: Our study concluded as the risk of Major Adverse Cardiac and Cerebrovascular Events (MACCE) is higher by approx. 20% in 1st year of follow up ($P<0.001$) of patients among the Zoster group, therefore Herpes Zoster is a marker of long term cardio vascular diseases risks.

Key Words: Herpes zoster, cardio vascular diseases, cardio vascular diseases risk, Acute myocardial infarction (AMI), stroke, Percutaneous coronary intervention(PCI).

Introduction:

The basis for increased cardiovascular events following acute infection is hypothesized to be endothelial dysfunction, characterized by atheromatous plaque rupture and the development of a prothrombotic environment [2]. As acute cardiovascular diseases (CVDs), specifically ischemic stroke and MI, are major causes of morbidity and mortality in the US and worldwide, understanding the basis for acute cardiovascular events and any potential for prevention becomes increasingly important [3]. Herpes zoster results from reactivation of dormant varicella zoster virus (VZV). Herpes zoster is an important disease as it affects 1 million Americans per year and is frequently complicated by prolonged, severe, disabling pain, a condition called post-herpetic neuralgia (PHN) [4,5]. Zoster-associated morbidity led to the introduction of a targeted vaccination program for individuals aged 60 y or greater in the US in 2006. The zoster vaccine has been shown to be effective in routine practice against incident zoster and PHN. Despite this, uptake of this vaccine has been disappointing (3.9%) following its introduction in the US, with important discrepancies in vaccine uptake by race and by income status [6]. Recent studies have proposed that the risk of stroke may be increased in the year following an acute episode of herpes zoster, possibly also mediated by VZV replication in arterial walls, resulting in cerebral maculopathy [7]. Most studies assessing the association between herpes zoster and stroke have been limited by residual confounding because comparisons were made between individuals who developed herpes zoster and those who did not and these populations have important differences in underlying vascular risk that are difficult to measure and account for. In a previous study, our research group used the self-controlled case series (SCCS) method, which eliminates between-person confounding, to demonstrate that there is an increased risk of stroke in the first 6 mo. following herpes zoster in the Indian population and that antiviral therapy might lessen this association [8]. One Indian cohort study, which may be limited by residual confounding, also suggested a longer-term increased risk of stroke and MI up to 24 y following acute herpes zoster [9]. To our knowledge, no previous study has determined the risk of MI in the period immediately following herpes zoster or assessed the role of zoster vaccination in the association between zoster and acute cardiovascular events.

Materials and Methods:

This was cross-sectional study carried out in Department of Dermatology, General Medicine, Cardiology and Neuro-medicine, Santiniketan Medical College and Hospital, Bolpur, Birbhum, West Bengal, India as well as at our private clinics. Ethical approval was obtained from the hospital.

Analysis:

Descriptive statistics were presented for the entire study population and stratified according to HZ-exposure status. Continuous variables were expressed as means±standard deviation (SD), medians, and minimum/maximum values. Categorical variables were presented as frequencies and percentages out of the available cases. Between-group comparisons of baseline covariates were performed using t-tests or Wilcoxon tests for continuous variables and chi-square tests or Fisher's exact test for categorical variables. Cumulative event distributions of the endpoints were presented using the Kaplan–Meier method, and was calculated for the entire study period (up to 17 years). Time to events was compared among subgroups with the logrank test. Multivariable Cox regression analyses were conducted to assess the relationship between HZ exposure and stroke, MI, and MACCE incidence over three follow-up periods (1 year, 5 years, and 15 years). Regression

analyses were conducted incorporating several variables of clinical importance, and those variables exhibiting statistical significance were included in the final model. Cox regression analyses were stratified according to matched pairs and adjusted for socioeconomic status, age, history of dyslipidemia, and prior AMI. Given the relatively wide caliper (±5 years) used for age matching, the age adjustment of this regression model was imperative to avoid any remaining confounding effects of age on the resultant data. Socioeconomic status, the history of dyslipidemia, and prior AMI also differed significantly between groups and were regarded as possible confounders. Proportional hazard assumption was tested by inspection of survival curves for categorical covariates and tested based on Shenfield residuals for the continuous covariates. A two-tailed P.

Results:

Overall, 200 subjects were diagnosed with HZ during the study period, 200 patients were included in this study (100 patients per group). The average age at zoster diagnosis was 45.7 (±18.0) years. Of these patients, 33.8 were male, 18% had diabetes mellitus, and 30.5% had hypertension as underlying diagnoses. The follow-up period did not differ significantly between the study groups, with a minimum of 0 and a maximum of 5 years, and a mean follow-up interval of 1.5 years. Cumulative MACCE survival at the end of the follow-up period was 54% in the HZ group as compared to 74% in the non-HZ group (P<0.001). The stroke cumulative survival rate was 88.8% in the HZ.

Table 1: Demographic characteristics of the cases according to Zoster exposure status.

Characteristics	Non HZ group, n=100 in %	HZ group, n=100 in %	P value
Male	34	34	
Female	66	66	
Age at Zoster, years			0.847
Mean ±SD	45.6±18.0	45.6±18.2	
Median	42.5	42.5	
Diabetes mellitus	18%	18%	
Hypertension,	30.5%	30.5%	
Dyslipidemia	7%	80%	<0.001
Prior stroke	0.5%	0.4%	0.563
Prior MI	2.2%	2.9%	<0.001
Smoking	21.8%	21.5%	0.637

Group as compared to 94.0% in the non-HZ group (P=0.062). The AMI cumulative survival rate was 68.7% in the HZ group and 90.0% in the non-HZ group (P<0.001). In a multivariable analysis adjusted for age, socioeconomic status, dyslipidemia, and prior AMI, we estimated the hazard ratio (HR) associated with prior HZ exposure compared to non-HZ subjects after 1, 5, and 15 years following exposure. The hazard ratio determines whether a patient in the HZ group at any given time has a greater, equal, or lower probability of experiencing MACCE during the next unit of time than a subject in the non-HZ group. As such, any value above 1, will demonstrate a higher probability of experiencing MACCE.

The HR for MACCE incidence in the HZ group was 1.19 (95% CI 1.01; 1.39, P=0.035) after 1 year, 1.07 (95% CI 0.96; 1.18, P=0.219) after 5 years, and 1.03 (95% CI 0.95; 1.13, P=0.451) after 15 years (Table 3). Analyses of the MACCE-free interval revealed a significant difference in survival between the HZ group and the non-HZ in the year following HZ exposure, but the difference was not significant after 5 years. Analyses of the stroke-free interval and MI-free interval can be found in the appendix, Analyses of stroke-free, MI-free, and MACCE-free survival were conducted to assess the potential impact of treatment with antiviral drugs within a month after

exposer to zoster (Acyclovir, Famciclovir and Valaciclovir) on HZ patients. The analyses revealed lower survival rates in subjects treated with antiviral medications.

Table 2. Post zoster vascular event survival, throughout the entire study period. *Multivariable regression is adjusted to gender, age, diabetes, hypertension, socioeconomic status, dyslipidemia, and prior AMI.

Parameter	Non HZ group,	HZ group,	P value
MACCE, survival %±SD	74%±0.02	54%±0.12	<0.001
Stroke, survival %±SD	94%±0.02	88.8%±0.03	0.062
Acute MI, survival %±SD	90%±0.02	67.8%±0.15	<0.001
Stroke or MI, survival %*±SD	84%±0.02	62%±0.13	<0.001

Table 3. Multivariable Cox regression for HZ exposure on the study outcome.

	1year from the exposure of zoster	5years from the exposure of zoster	15years from the exposure of zoster
MACCE			
Hazard ratio (95% CI)	1.19 (1.01; 1.39)	1.07 (0.96; 1.18)	1.03 (0.95; 1.13)
P value	0.035	0.219	0.451
Stroke			
Hazard ratio (95% CI)	0.78 (0.50; 1.21)	1.04 (0.83; 1.31)	1.13 (0.93; 1.37)
P value	0.271	0.748	0.208
AMI			
Hazard ratio (95% CI)	1.30 (0.95; 1.78)	1.07 (0.87; 1.33)	1.02 (0.85; 1.22)
P value	0.098	0.486	0.867

The HR values corresponding to stroke and AMI risk when comparing HZ and non-HZ subjects were estimated in a multivariable analysis adjusted for age, socioeconomic status, dyslipidemia, and prior AMI. For stroke the estimated HR was 0.78 (95% CI 0.50; 1.21, P=0.271) after 1 year, 1.03 (95% CI 0.82; 1.30, P=0.791) after 5 years, and 1.12 (95% CI 0.93; 1.36, P=0.226) after 15 years. With respect to AMI the estimated HR was 1.30 (95% CI 0.95; 1.78, P=0.098) after 1 year, 1.07 (95% CI 0.87; 1.33, P=0.486) after 5 years, and 1.02 (95% CI 0.85; 1.22, P=0.867) after 15 years (Table 3).

Discussion:

In the current analysis, we investigated whether suffering from an acute episode of HZ is associated with increased long-term vascular risk using an extensive HMO computerized database. Tough they failed to reach significance after 5 years of follow up, our results nonetheless show that HZ infection trended towards a long-term increased risk of ischemic events in our cohort, including both cerebrovascular and coronary events. The risk of MACCE was 19% higher among HZ sufferers in the first year of follow up, and this risk was sustained for at least 4.4 years following the episode. It was not affected by the administration of antiviral agents during the HZ episode. Previous studies have primarily reported increased short-term (weeks to months) stroke risk after an HZ episode. Schink et al. [17] demonstrated that stroke risk increased in the first week following HZ infection and then fell over the subsequent 6–12-month follow-up period. Minassiant et al. [18] observed an increase in stroke incidence a few weeks after HZ infection and a gradual decline in the risk of stroke in the following weeks. Sreenivasan et al. [19] reported a peak in stroke incidence 2 weeks following HZ infection when analyzing a vast database (4.6 million enrollees) in Denmark followed by the moderation of this risk over a 1-year period. A similar pattern of increased risk of stroke in the following weeks after HZ infection and then declining risk during the following months was also demonstrated by Langan et al. [8,20]. A meta-analysis conducted by Liu et al.12 summarizing data from eight studies likewise showed a short-term increase in stroke risk followed by a decline in such risk following HZ infection, with the highest level of risk during the first 2 weeks (risk ratio [RR]: 2.36), with the RR falling to 1.56, 1.17, and 1.03 at 1, 3, and 6 months,

respectively. Interestingly, Marra et al. [22] found no association between HZ and stroke over a long 3-year follow-up interval. Early post-HZ stroke and AMI risk has been attributed to a hypercoagulable state caused by prothrombotic autoimmune antibodies such as anticardiolipin forming during the HZ infection [14], circulating immune complexes, and systemic inflammation [15]. In their retrospective study, Breuer et al. showed that the HR for TIA and MI but not strokes were increased in all patients with HZ [9,25]. However, HZ patients included in this study had significantly more cardiovascular risk factors (diabetes, hypercholesterolemia, hypertension, smoking) than matched control subjects, which accounted for a major bias in the long term follow-up of vascular events in HZ subjects. This can also be said of the Danish study aforementioned though both studies identified the risk of stroke and TIA to be highest in those whose HZ occurred under the age of 40 years [10,16]. While our study did not segregate age groups, our robust adjustment method mitigated this bias and gave us a more neutral analysis of the long term effects of HZ on all major adverse cardiac and cardiovascular events, including stroke, TIA, MI. In their prospective study, Curhan et al. demonstrated similar results to our observations and showed a long term implication of HZ in stroke and coronary heart disease [17]. Tough they based their analysis of of self-reported information on HZ without considering treatment, our findings expand on their results, and together imply that the increased risk is not limited to the cerebrovascular system but instead represents an elevated level of systemic cerebrovascular and coronary risk [16]. It is difficult to determine from our results whether this increased risk is caused by the HZ event, potentially resulting from inflammatory and prothrombotic changes that may persist for years, or whether the HZ episode is instead a marker for increased vascular risk, with patients exhibiting greater vascular risk when being exposed to HZ. Tough former studies on the short-term [7,11,18,19] and long-term [10] cardiovascular outcomes after antiviral use in HZ patients exhibited significant positive effects, our results tend to show the opposite effect, even suggesting a negative outcome of antiviral treatments on long-term survival.

This should be put in perspective as our study design did not allow us to review detailed information regarding treatment options, treatment plans, or patients' therapeutic compliance over a 15-year follow-up period. However, we should also consider that in clinical practice, antiviral agents are more frequently given to HZ patients with underlying comorbid conditions. Tough they received treatment in the acute phase of the infection, the long-term residual effects of HZ may have negatively impacted already fragile vascular homeostasis in these individuals, further decreasing long-term survival. Therefore, we believe that it is more reasonable to interpret HZ as a marker of high vascular risk rather than a causative factor. The current study has some limitations. First, the case definition was based on administratively collected data, leaving cases of undiagnosed HZ patients unrecorded in the database. Such misclassification can potentially decrease the effect size toward the null hypothesis. Second, our data did not include HZ vaccination status, which could be a limitation given that recent literature has shown a decreased risk of neurologic post-infection sequelae in vaccinated patients20. Third, because our study focused mainly on the impact of HZ on vascular effects and did not comprise detailed information on vaccinations and treatments, only limited data regarding the long-term influence of HZ therapeutics on cardiovascular pathologies could be collected. Lastly, missing clinical details, such as HZ dermatome location, precluded any in-depth analysis of the exposure type or its implications. However, our study has some noteworthy strengths. This is the first study to explore the risk of cardiovascular events in HZ patients compared with non-HZ patients over a 15-year period. In addition, the unique setup of a centralized healthcare system with a single tertiary hospital treating all the acute patients in the region allows for the reliable evaluation of vascular risk in a very large cohort of patients. The findings of our study suggest that HZ is a long-term vascular risk marker. Based on our observation, clinicians should consider reevaluating the vascular risk profile of patients recovering from HZ. Further studies are warranted to determine how a history of HZ should be incorporated into cardiovascular risk calculators and to evaluate the long-term impact of vaccines and mitigation

strategies on such risk. Although our administrative data, so misclassification of exposures and outcomes is possible. However, provided the exposure and outcome are ascertained independently, any random misclassification in SCCS analyses would tend to bias findings towards the null. [30]

Conclusion:

Our study concluded as the risk of Major Adverse Cardiac and Cerebrovascular Events (MACCE) is higher by approx. 20% in 1st year of follow up($P<0.001$) of patients among the Zoster group, therefore Herpes Zoster is a marker of long term cardio vascular diseases risks.

Source of funding: None

Conflict of interest: None.

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