Association of Short- and Medium-Term Particulate Matter Exposure with Risk of Mortality after Spontaneous Intracerebral Hemorrhage

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Objective: We investigated the association of short- and medium-term particulate matter (PM) exposure with risk of mortality in patients with spontaneous intracerebral hemorrhage (ICH) identified according to strict etiologic criteria. *Methods:* We conducted a retrospective analysis of prospectively collected data from consecutive patients with spontaneous ICH admitted to the emergency department of the University Hospital of Verona from March 2011 to December 2014. Outcome measures were mortality within 1 month after ICH and significant hematoma expansion (HE) defined as an absolute growth of more than 12.5 mL or a relative increase of more than 50% from baseline to follow-up computed tomography scan. *Results:* A final number of 308 patients were included. In the adjusted model, higher $PM_{2.5}$ and PM_{10} values in the last 3 days (odds ratio [OR] 1.827, 95% confidence interval [CI] 1.057-3.159, $P = .031$ and OR 1.949, 95% CI 1.025-3.704, $P = .042$, respectively) and in the last 4 weeks (OR 4.975, 95% CI 2.174-11.381, $P < .001$ and OR 9.781, 95% CI 3.425-27.932, $P < .001$, respectively) before ICH were associated with higher mortality rate. No association was found between PM exposure and significant HE. *Conclusions:* PM exposure in the short- and medium-term before spontaneous ICH was associated with risk of 1-month mortality, independent of predictors such as age, sex, stroke severity, intraventricular hemorrhage, ICH volume, ICH location, ICH etiologic subtype, significant HE, antithrombotic therapy, atrial fibrillation, and blood glucose levels. **Key Words:** Intracerebral hemorrhage—particulate matter—air pollution—mortality—SMASH-U.

Introduction

Increased values of air pollutants, especially particulate matter (PM) exposure, may be associated with respiratory and cardiovascular diseases, as well as general morbidity and mortality.[1-3] While several studies showed a consistent association between exposure to PM with aerodynamic diameter less than 10 μm (PM_{10}) and less than 2.5 μm ($PM_{2.5}$) and ischemic stroke mortality, the association of PM exposure with mortality after intracerebral hemorrhage (ICH) is still uncertain.[4-6] Heterogeneity in the association between PM exposure and stroke subtypes might be caused by many factors. First, there were fewer estimates for ICH, reflecting the lower incidence

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of this subtype, and therefore wider confidence intervals (CIs) for these estimates. Second, because much of the existing literature are based on linkage of administrative data (i.e., International Classification of Diseases, Ninth and Tenth Revision codes), in the majority of studies ischemic stroke and ICH and their subtypes have been analyzed as a combined outcome despite the clear possibility that air pollution may affect underlying pathophysiological pathways differently. Only a few studies have separately analyzed ischemic and hemorrhagic stroke, and a handful have considered subtypes of hemorrhage (i.e., ICH versus subarachnoid hemorrhage). To our knowledge, no reliable data have been published about the possible association between PM exposure and mortality in patients with spontaneous ICH identified according to strict etiologic criteria.

ICH is the deadliest stroke subtype with 1-month mortality rates exceeding 40%.[7,8] Initial hematoma volume remains the strongest predictor of 30-day mortality and functional outcome.[9] Nevertheless, approximately 30% of patients continue to bleed and demonstrate significant hematoma expansion (HE) during hospitalization, which further aggravates outcome.[10-13] To date, no reliable data have been reported about a possible association between PM exposure and significant HE.

Therefore, the main aim of this study was to investigate a possible association between short- and medium-term air pollution exposure and 1-month mortality after spontaneous ICH in patients identified by use of an etiologic classification system. A secondary aim was to explore a possible association of short- and medium-term PM exposure with significant HE.

Materials and Methods

Study Design

We conducted a retrospective analysis of prospectively collected data from consecutive patients with ICH, who were admitted to the emergency department of the University Hospital of Verona from March 2011 to December 2014. The time interval was defined based on study feasibility and data availability.

We included all patients with an available initial computed tomography (CT) scan within 12 hours after symptoms onset and follow-up CT scan within 48 hours after the baseline CT scan.

Patients with spontaneous ICH were selected excluding the patients with nonstrokes (primary subdural/epidural hematoma or traumatic ICH or hemorrhage due to a tumor) and those with strokes non-ICH (primary subarachnoid hemorrhage with or without ICH and hemorrhagic transformation of a cerebral infarction with or without thrombolytic therapy nonstroke) according to the structural vascular lesions, medication, amyloid angiopathy, systemic disease, hypertension, or undetermined (SMASH-U) classification system.[14]

The data about air pollution were obtained from the Regional Environmental Protection Agency (ARPAV) of the Veneto Region (Italy).[15] The ARPAV has permanent monitors, which provide daily data on air pollution (24 hours averages) of the entire district of the town of Verona (a geographical area with a population of approximately 270,000 inhabitants) and include both the center of the town and its suburbs. All measurements of the different pollution agents are regularly validated by standardized quality control procedures.[15] The analyzers used for PM_{10} and $PM_{2.5}$ are based on a filtering pretreatment of air sample, aspirated by an appropriate pump system, and the quantitative assessment is then performed with a gravimetric method, as specified in ARPAV website.[15] The "short-term" exposure has been defined as exposure in the last 3 days before ICH, and the "medium-term" exposure has been defined as exposure in the last 4 weeks, in agreement with the Joint World Health Organization/Convention Task Force on Health Aspects of Air Pollution.[16] All patients living in our selected geographical area (i.e., the town of Verona and suburbs), for which complete data of 24-hour PM levels were available, were finally included in our study, whereas those who were not resident in the town or in the immediate neighborhood (i.e., within a 10-km radius from the air-quality monitoring station) were excluded.

Outcome Measures

Mortality within 1 month after ICH was identified as the primary outcome measure. The secondary outcome measure was significant HE, which is defined as an absolute growth of more than 12.5 mL or a relative increase of more than 50% from baseline to follow-up CT scan.[11,13] ICH volumes were estimated with the standard ABC/2 method, in which A is the greatest diameter on the largest hemorrhage slice, B is the diameter perpendicular to A, and C is the approximate number of axial slices with hemorrhage multiplied by the slice thickness.[17]

Statistical Analysis

Differences between the cohorts were explored using the Mann–Whitney *U* test for continuous variables. Differences between proportions were assessed by Fisher's exact test or the χ^2 test, when appropriate. Proportions were calculated for categorical variables, by dividing the number of events with the total number after exclusion of missing/unknown cases. Continuous variables were reported as median and interquartile range values. A value of $P < .05$ was considered as statistically significant. Distribution was tested for normality using Shapiro–Wilk test, and non-normally distributed parameters were logarithmically transformed before multivariate analyses.

The possible association of PM levels with the rate of 1-month mortality was estimated with an adjusted analysis (logistic regression) using a forward stepwise method