

Higher mortality due to intracerebral hemorrhage in dialysis patients: A comparison with the general population in Japan

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Abstract

Background

Cerebrovascular diseases, including intracerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage, remain prevalent causes of morbidity and mortality among dialysis patients. Their mortality rate for cerebrovascular diseases is roughly 3 times higher than that in the general population. However, whether mortality rates for all subtypes of cerebrovascular diseases are equally higher has not been evaluated. The aim of this study was to determine the mortality rate for each stroke subtype, comparing dialysis patients and the general population in Japan.

Methods

We used mortality data reported by the Japanese Society for Dialysis Therapy and national Vital Statistics data between 2008 and 2009. We calculated standardized mortality ratios and compared the mortality rates for stroke subtypes including intracerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage.

Results

During the 2-year study period, 51 994 and 933 deaths from intracerebral hemorrhage, 79 124 and 511 deaths from cerebral infarction, and 24 957 and 147 deaths from subarachnoid hemorrhage were recorded per 252 million person-years and per 546 474 dialysis patient-years, respectively. Standardized mortality ratios among dialysis patients relative to the general population were 3.8 (95% confidence interval, 3.6–4.1), 1.3 (1.2–1.4), and 1.3 (1.1–1.6) for intracerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage, respectively. Intracerebral hemorrhage was the highest cause

of mortality in the dialysis population, although cerebral infarction was the highest in the general population.

Conclusions

Relative to the general population in Japan, Japanese dialysis patients had higher mortality rates, especially for intracerebral hemorrhage.

Key Words: Cerebral infarction, Dialysis, Epidemiology, Intracerebral hemorrhage, Mortality, Standardized mortality ratio, Subarachnoid hemorrhage

Introduction

Cerebrovascular diseases, including intracerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage, remain important causes of morbidity and mortality among dialysis patients. Although the percentage of patients who die as a result of cerebrovascular diseases has gradually decreased, it remains the fourth leading cause of death among Japanese dialysis patients, according to the Japanese Society for Dialysis Therapy (JSDT) registry (1).

We previously reported that the mortality rate for cerebrovascular diseases in dialysis patients is approximately three times higher than that in the general population (2). However, it is not clear whether all subtypes of cerebrovascular diseases have equally higher rates, as this has not been evaluated. Analyses stratified by stroke subtype are considered useful and important for establishing effective prevention strategies in dialysis patients.

The aim of this study was to compare mortality rates for several stroke subtypes between dialysis patients and the general population in Japan. To this end, we analyzed annual mortality rates for several types of cerebrovascular diseases in Japanese dialysis patients and compared them with rates derived from Japanese national Vital Statistics data.

Materials and Methods

Sources of data

Mortality data of dialysis patients were extracted from annual data reported by the Renal Data Registry Committee of JSDT for 2008 and 2009 (3, 4). The JSDT registry

data collection techniques and characteristics of the dialysis population have been described in detail elsewhere (1, 5). Briefly, the JSDT registry collects data every year by sending questionnaires to all dialysis facilities in Japan. This registry collects information on medical history, treatment condition, and outcome for individual dialysis patients. As patient characteristics may be associated with cerebrovascular mortality, a brief summary is given here. For the year ending December 31, 2008, the percentage of patients treated by hemodialysis and peritoneal dialysis was 96.7% and 3.3%, respectively (5). Primary diseases causing end-stage kidney disease, in the order of decreasing incidence, were chronic glomerulonephritis (39.0%), diabetic nephropathy (34.2%), unspecified primary diseases (7.6%), nephrosclerosis (6.8%), polycystic kidney disease (3.4%), chronic pyelonephritis (1.1%), systemic lupus erythematosus nephritis (0.8%), and rapidly progressive glomerulonephritis (0.7%) (5). Among them, the percentage of patients who had histories of cerebral hemorrhage and cerebral infarction was 4.6% and 12.8%, respectively. Mean levels of hemoglobin, serum albumin, and C-reactive protein were 10.36 (standard deviation (SD) 1.29), 3.67 (SD 0.45), and 0.61 (SD 1.87), respectively (3).

Mortality data for the general population were obtained from a national Vital Statistics survey. The National Vital Statistics Survey Form consists of five types of forms: Live Birth Form, Death Form, Fetal Death Form, Marriage Form, and Divorce Form. We used data from the Death Form, which is based on Notification of Death, for 2008 and 2009 (6, 7).

All data were stripped of patient identifiers. The study was conducted according to Japanese privacy protection laws, and the ethical guidelines for epidemiological

studies published by the Ministry of Education, Science and Culture, and the Ministry of Health, Labor and Welfare in 2005.

Case definitions

Mortality due to cerebrovascular diseases was included in the analyses of both the JSDT and national Vital Statistics data only if cerebrovascular disease was the underlying cause of death. Stroke subtypes were defined according to the JSDT definition, which uses the 10th modified edition of the International Classification of Diseases (ICD-10) codes (8): intracerebral hemorrhage (ICD-10 code I61), cerebral infarction (ICD-10 code I63), and subarachnoid hemorrhage (ICD-10 code I60). It is important to note that the planned analyses did not compare case fatality rates, which is the ratio of deaths among patients suffering from cerebrovascular diseases over a certain period of time, but rather annual mortality due to cerebrovascular diseases.

Data analyses

Both dialysis patients and individuals from the general population were categorized into six age groups: 0–14, 15–29, 30–44, 45–59, 60–74, and ≥ 75 years.

Calculation methods have been described previously in detail (9).

First, we analyzed annual mortality rates for each type of cerebrovascular disease, which included only cases with a definite cause of death. Mortality rates were calculated as the number of deaths divided by the number of person-years accumulated during the study period. An estimate of the number of person-years during the study period was obtained by multiplying the number of the population at the mid-point by 2 (10). To

compare mortality rates between dialysis patients and the general population, the mortality rate for each type of cerebrovascular disease among the general population was adjusted for age distribution of dialysis patients.

We next calculated standardized mortality ratios (SMRs) for each type of cerebrovascular disease. SMRs were calculated by dividing observed numbers of deaths by expected numbers. Expected numbers were calculated by multiplying the total number of person-years during the study period by the corresponding age-specific mortality rate for the general population. Confidence intervals (CIs) for the SMRs were calculated using the normal approximation to the Poisson distribution. The SMR can be interpreted as the relative difference in the mortality rate among dialysis patients compared with that of the general population.

Finally, we calculated the mortality rate for each cerebrovascular disease in the dialysis population stratified by dialysis vintage. Dialysis vintage was defined as the duration of dialysis treatment after its initiation, and was categorized with respect to its duration: less than one year, one to four years, five to nine years, ten to fourteen years, and fifteen years or more. It is important to note that the analyses stratified by dialysis vintage were unadjusted given the nature of the design.

All calculations were performed with Microsoft Excel (Redmond, WA, USA) and CIA (Confidence Interval Analysis, version 2.2.0, University of Southampton, UK).

Results

During the 2-year study period, 51 994 and 933 deaths from intracerebral hemorrhage, 79 124 and 511 deaths from cerebral infarction, and 24 957 and 147 deaths

from subarachnoid hemorrhage were recorded in 252 million person-years and 546 474 dialysis patient-years, respectively. Age-adjusted mortality rates for intracerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage were 4.48, 7.44, and 2.00 per 10 000 person-years in the general population, respectively, and 17.07, 9.35, and 2.69 per 10 000 person-years in the dialysis populations, respectively (Table 1). Mortality rates for intracranial hemorrhage were markedly higher in dialysis patients compared with the general population, even among younger age groups (Figure 1A). Mortality rates for cerebral infarction or subarachnoid hemorrhage were slightly higher than those in the general population (Figure 1B and C). SMRs for intracerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage were 3.8 (95% CI, 3.6–4.1), 1.3 (95% CI, 1.2–1.4), and 1.3 (95% CI, 1.1–1.6), respectively, for dialysis patients relative to the general population. Intracerebral hemorrhage had a higher mortality rate in all categories of dialysis vintage than other subtypes of cerebrovascular diseases (Table 2).

Discussion

The present study found that mortality due to intracerebral hemorrhage was markedly higher in Japanese dialysis patients compared with that in the general population, while mortality due to cerebral infarction or subarachnoid hemorrhage was slightly higher. In addition, among the three stroke subtypes, intracerebral hemorrhage had the highest mortality in Japanese dialysis patients at any dialysis vintage. These findings directly contrast with those found for the general Japanese population, in which cerebral infarction had the highest mortality rate. This may suggest that prevention and

treatment of intracerebral hemorrhage is one of the most important issues for reducing mortality due to cerebrovascular diseases in dialysis patients.

There is limited information regarding stroke mortality in dialysis patients compared to the general population. Data from the European Renal Association-European Dialysis and Transplant Association Registry have shown that the age- and sex-standardized mortality rate for stroke was 8.3 (95% CI 8.0-8.5) times higher in incident dialysis patients than in the general population (11). However, mortality rates for each stroke subtype were not mentioned. A recent retrospective study in a single stroke center in Japan reported that hemodialysis patients had a higher risk of all-cause death within 14 days of intracerebral hemorrhage than non-hemodialysis patients (12). This finding is consistent with our large-scale, nationwide study.

Previous studies have shown that hemorrhagic stroke was associated with higher fatality rates, which is the ratio of deaths among patients presenting with a particular condition, than ischemic stroke (13-16). However, the incidence of hemorrhagic stroke is reportedly lower than ischemic stroke in many countries, such as the United States (14, 17), the United Kingdom (15), and Taiwan (16). In Japanese dialysis patients, the incidence of intracerebral hemorrhage has previously been reported to be higher than that of cerebral infarction (13, 18-21), but more recently, the incidence of cerebral infarction was higher than that of cerebral hemorrhage (22) as in other countries, which might reflect more conservative dialysis circuit anticoagulation, better blood pressure control, a more Westernized lifestyle (13, 22), and increasing diabetic nephropathy. In 1998, the proportion of patients with diabetic nephropathy as the primary disease was 7.4% of all dialysis patients. The proportion continued to increase, and reached 34.2% in 2008 (5).

While this trend needs to be investigated in more detail in a nationwide survey, considering that the incidence of hemorrhagic stroke is lower than that of ischemic stroke, mortality due to intracerebral hemorrhage appears to be high in Japanese dialysis patients.

Dialysis patients are at higher risk of bleeding due to several factors including uremic platelet dysfunction and anemia (23, 24). For example, anemia may potentiate bleeding via several effects on platelet function in dialysis patients. Circulating red blood cells displace platelets toward the vessel wall, which helps facilitate their contact with the subendothelium at sites of damage. Red blood cells also enhance platelet function by releasing adenosine diphosphate (ADP) and thromboxane A₂ (23, 24). Moreover, hemodialysis patients have bleeding risks due to anticoagulants used during dialysis treatment. Because Japanese dialysis patients were mostly treated by hemodialysis, improving these conditions might be needed to decrease mortality from intracerebral hemorrhage.

In the general Japanese population, mortality from stroke has declined continuously from the 1960s to the 2000s as a result of the nationwide approach to hypertension prevention and control (25). Although it is unclear from the JSDT database whether mean blood pressure levels have declined over the last three decades, dialysis patients might need to control blood pressure more strictly to decrease mortality from cerebral hemorrhage, because hypertension is also a risk factor for stroke in these patients (21). A more detailed analysis of risk factors for stroke subtype mortality among Japanese dialysis patients is warranted.

Some limitations of the present study should be noted. First, we included in the analyses only those with cerebrovascular diseases which were noted as the definite

underlying cause of death, because we did not have information on deaths suspected to result from cerebrovascular diseases. Definite causes of death were available for only one third of the total deaths in the JSDT registry; thus, mortality from subtypes of cerebrovascular diseases could be underestimated. Second, the validity of diagnoses could not be confirmed. However, as our study used ICD-10 codes to define the cause of death in both surveys, it is unlikely that this would introduce bias in our results. Third, SMRs were adjusted only for age. Finally, mortalities stratified by vintage were unadjusted because no information was available.

Despite these limitations, this study has several strengths. Our study used data from a national Vital Statistics survey and a nationwide survey of Japanese dialysis facilities. Both surveys are an almost complete national census. In addition, to the best of our knowledge, we are the first to demonstrate that intracerebral hemorrhage is still the highest cause of mortality among Japanese dialysis patients, in contrast to the general population.

Conclusions

Our study demonstrated that, among stroke subtypes, intracerebral hemorrhage was the highest cause of mortality among Japanese dialysis patients, in contrast to the general population. Further studies, such as those to determine adequate blood pressure control, improving the nutritional state, and considering anticoagulation treatment, are needed to decrease mortality from intracerebral hemorrhage in dialysis patients.

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Figure legend

Figure 1. Mortality rates due to intracerebral hemorrhage (A), cerebral infarction (B), and subarachnoid hemorrhage (C) among dialysis patients (black line) compared with the general population (gray line). Data are stratified by age.