ABSTRACT

Background

Infection is the second leading cause of death in maintenance hemodialysis patients, but available data about the effect of glycemic control on infection is scarce in diabetic hemodialysis patients.

Subjects and methods

Patients with maintenance hemodialysis (n=1551, 493 diabetic patients) were enrolled in this prospective cohort study on December 2009 and followed up for 3 years. Infection-related hospitalization (IRH) during follow-up was abstracted from the medical records. Kaplan-Meier and Cox regression analysis was used to examine the association between diabetes or glycemic control and IRH.

Results

The IRH risk was significantly higher in hemodialysis patients with diabetes than those without it, in particular, in the diabetic patients with poor control of HbA1c level (HbA1c ≥ 7.0%) by Kaplan-Meier analysis. When the patients with ≥ HbA1c 7.0% were divided into two groups using a median value of HbA1c, the risk of IRH was significantly higher in the groups with poorest glycemic control (HbA1c ≥ 7.4%), older age, or lower albumin level. The multivariable-adjusted hazard ratio for the risk of IRH

was not increased in the second criteria of HbA1c (HbA1c 7.0-7.3%), but was significantly increased in the group with poorest glycemic control (HbA1c ≥ 7.4%), compared with those in the good control criterion (HbA1c < 7.0%).

Conclusions

Diabetes is a risk factor for IRH among maintenance hemodialysis patients, but the relation between glycemic control and infection risk is not a linear. There might be possibility to increase the risk of infection depending on the glycemic control threshold.

Introduction

In dialysis population, infection is the second most common cause of death, after cardio vascular disease, and is also common cause of hospitalization (1-4). In addition, the mortality ratio due to infection is significantly higher in dialysis patients than general population. Previous report shows pulmonary infectious mortality was 14 to 16 times higher rate compared to the general population (5). A recent Japanese report revealed pneumonia accounts for about half of the cause of infection-related death in dialysis patients among a variety of infectious disease, and the mortality rate due to pneumonia is four-fold higher in the 60-74-year-old age group compared to the general population (6).

On the other hand, patients with diabetes mellitus (DM) are considered to be more susceptible to several types of infections, including pneumonia, urinary tract infection, and skin infection (7-9). As for the reasons why the DM is related with the development to infection, it is conceivable that DM is associated with immune dysfunction (10, 11). However, in dialysis patients, it is somewhat controversial whether relative risk factor for infection-related hospitalization (IRH) is different among subjects with and without diabetes, controlling for potential confounding factors (9, 12-17). In addition, there are limited data on the association between infection and glycemic control in diabetic

patients on hemodialysis.

The aim of this study was to examine 1) association between DM and factors related for IRH, and 2) the impact of glycemic control on IRH risk among diabetic patients on maintenance hemodialysis.

Subjects and Methods

This Dialysis Cohort study (MID study) is a prospective observational study of maintenance HD patients from 27 dialysis centers. A total of 1,551 patients, who received HD therapy for more than 3 months, were enrolled in this cohort study in December, 2009 and were followed up for 3 years. Exclusion criteria were 1) patients with acute renal failure, 2) hospitalized patients at enrollment, 3) patients under 18 years of age and 4) patients who did not agree to this study. Information on physical characteristics, laboratory data, basal renal diseases, comorbidities, and medications was collected by doctors in each dialysis center at the start of the study. Cardiovascular events (acute myocardial infarction, de novo angina pectoris, revascularization, congestive heart failure, stroke, and limb amputation), infections, the new onset of malignancies, and all causes of hospitalization and death were checked at the events by nursing staff or medical doctors during the follow-up periods using check sheets. Check

sheets were collected and medical records at hospitalization were confirmed by T.T. & Y.S. annually. In this study, only the first IRH was counted.

A patient was considered diabetic if the primary cause of ESRD was diabetes, diabetes mellitus was a comorbidity, oral hypoglycemic agents or insulin therapy were prescribed, or hemoglobin A1c (HbA1c) was ≥ 6.5% at baseline. The value for HbA1c was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following formula (18).

HbAlc (%) =HbAlc (Japan Diabetes Society) (%) + 0.4%

Survival time was defined as the time from enrollment to individual outcomes, the data for which were collected longitudinally during the course of the study follow-up until December 2012.

Statistical analysis

Descriptive analyses were calculated to describe variables such as the patient characteristics of groups distributed according to glycemic control. Crude IRH free rate in the each group was determined using Kaplan-Meier analysis with the log-rank test. Cox regression analysis using backward variable selection with variable exit criteria set was used to progressively adjust for baseline covariates. All statistical analyses were

performed with SPSS Statistics 20 (IBM Company, Chicago, USA).

Ethical Considerations

Although this was an observational study, Institutional Review Boards approved the present study (UMIN00000516). Data collection was performed in a manner that maintained patient anonymity.

Results

Patient Population

A total of 1,551 patients on hemodialysis had been identified by December 31, 2009. At baseline, there were 493 patients with diabetes and 1058 patients without it. Table 1 shows baseline patient characteristics according to the glycemic control. Patients without diabetes had more years since the initiation of hemodialysis than those with diabetes, as well as less past history of cardiovascular disease.

In the 3 years after January 1, 2010, 278 patients died, 124 moved to other dialysis facilities, and 21 underwent kidney transplantation. The kinds of infection were the following; pneumonia (n=97), gastrointestinal (n=46), soft tissue (n=21), genitourinary (n=12), vascular access associated (n=11), septicemia (n=10), joint (n=5) and other

(n=24).

Analysis for IRH in according to age, albumin level, and so on

90 of 493 patients with DM (7.80 /1000 patients per year), 136 of 1058 patients without DM (5.23/1000 patients per year) developed IRH during the 3-year follow-up, respectively. Figure1 shows that the IRH free rate was significantly lowest in A1c > 7.0 groups patients than in patients with other groups (Kaplan-Meier analysis, Log-rank test, P=0.003). In the next, we divided the patients with ≥ HbA1c 7.0% into two groups, using a median value of HbA1c in these patients, and evaluated the risk for IRH. Unadjusted Cox proportional hazard models showed the risk of IRH was significantly higher in the groups with poorest glycemic control (HbA1c ≥ 7.4%), older age or lower albumin level (< 3.5g/dL). The multivariable-adjusted hazard ratio for the risk of IRH was not increased in the second criteria of HbA1c (HbA1c 7.0-7.3%), but was significantly increased to 2.612 (95% CI 1.396-4.885) in the group with poorest glycemic control (HbA1c ≥ 7.4%), compared with those in the good control criterion of HbA1c level (HbA1c < 7.0%) (table2).

Discussion

This prospective cohort study revealed poor glycemic control (HbA1c ≥ 7.4%) was associated with IRH in maintenance hemodialysis patients. IRH was more frequently observed in hemodialysis patients with diabetes compared with those without diabetes. However, the association between glycemic control and IRH in diabetic patients was not linear and only patients group with poorest glycemic control had an increased risk for IRH.

Previous studies describe diabetic patients are more susceptible to several infections and they have more frequently experienced hospitalization due to these infections. Diabetic patients on hemodialysis therapy are also reported to have an increased risk of infection compared with non-diabetic ones. However, studies aiming at investigating impact of glycemic control for risk factors of infection in hemodialysis patients are limited. Mittman et al. (19) reported the levels of HbA1c were not associated with infections in diabetic patients on hemodialysis, but this report had several limitations. The study was performed in a single center, and they enrolled only a small number of patients (only 100 diabetic hemodialysis patients). On the other hand, Williams et al. (20) found that extremely high and low HbA1c values were associated with hospitalization risk in diabetic hemodialysis patients. In this study, in addition to poor glycemic control, other reported risk factors for IRH, such as age and serum albumin

level (21), were detected. Finally, we found an increased risk only with uncontrolled diabetes patients by a multivariable-adjusted analysis.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines (NKF KDOQI Guidelines) (22, 23) recommend the target level of HbA1c is < 7%in treating diabetic dialysis patients in similar to general population (24). Recently, Hill et al. report results of a meta-analysis of studies evaluating associations between HbA1c level and mortality in diabetic patients treated on hemodialysis. Baseline HbA1c levels ≧ 8.5% was associated with hazard ratios for death of 1.14 (95% CI, 1.09-1.19) adjusted for age, sex, diabetes type, time on hemodialysis therapy, and hemoglobin concentration (25). Our study suggest that HbA1c level could be < 7.4% to prevent IRH.

Our study does have some strengths. First, this study is first prospective report which examined the relationship between the risk of infection and glycemic control. Second, multivariate analyses on the risk of IRH were performed adjusting for some reported risk factors of hospitalization with infection in other than diabetes (age, serum albumin level, type of vascular access, pulmonary disease, decreased hematocrit levels, higher use of erythropoietin (12-15).

In considering about infection in hemodialysis patients, some different points exist

among countries and studies. First, patients receiving hemodialysis are at risk for infection associated with vascular access, but there were not so many IRH related to vascular access in Japan. It might be a reason why approximately 90% of hemodialysis patients in this study had an endogenous fistula on their arm. Second, our population is composed of relatively long-term hemodialysis patients. Death due to infection in early stage of hemodialysis introduction may be excluded in this study. One limitation in this study is observational, but not interventional one. HbA1c level also has limitations as a measure of glycemia, particularly in the dialysis population. Inaba et al. reported glycated albumin is better glycemic indicator than HbA1c in dialysis patients (26), and Peacock et al. revealed HbA1c underestimated in evaluating the glycemic control level in hemodialysis patients with diabetes compared to glycated albumin (27).

In conclusion, diabetes is a risk factor for IRH and poor glycemic control clearly increases such risk among diabetes patients.

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