



A prime determinant in selecting dialysis modality: peritoneal dialysis patient survival

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The number of patients with end-stage renal disease (ESRD) has rapidly increased, as has the cost of dialysis. Peritoneal dialysis (PD) is an established treatment for ESRD patients worldwide; it has a variety of advantages, including autonomy and flexibility, as well as economic benefits in many countries compared to hemodialysis (HD). However, the long-term survival rate of PD remains poor. Although direct comparison of survival rate between the dialysis modalities by randomized controlled trials is difficult due to the ethical issues, it has always been a crucial point when deciding which dialysis modality should be recommended to patients. Recently, in many countries, including the United States, Brazil, Spain, Australia, and New Zealand, the survival rate in PD patients has significantly improved. PD patient survival in Korea has also improved, but Korean PD patients are known to have higher risk of mortality and major adverse cardiovascular, cerebrovascular events than HD patients. Herein, we further evaluate why Korean PD patients had worse outcomes; we suggest that special attention should be paid to patients with diabetes, coronary artery disease, or congestive heart failure when they choose PD as the first dialysis modality in order to reduce mortality risk.

Keywords: Cardiovascular diseases, Hemodialysis, Mortality, Peritoneal dialysis

Introduction

The number of end-stage renal disease (ESRD) patients requiring dialysis treatment has been rapidly increasing worldwide over the past few decades. Korea is one of the countries with the highest increase in incidence (120%, from 2000/2001 to 2012/2013) and prevalence of ESRD (from 585 per million in 2000/2001 to 1,442 per million in 2012/2013) [1].

Most ESRD patients choose between hemodialysis (HD) and peritoneal dialysis (PD) at initiation of renal replacement therapy. It is crucial to address which modality is a better option for long-term mortality and morbidity outcomes in ESRD patients. Multiple studies have been conducted to investigate these issues, but the results were not conclusive [2]. In Korea, we reported that overall mortality rate and incidence of cardiovascular events are higher in incident PD patients than in HD patients [3,4].

Short-term PD patient survival rate is generally considered superior to that of HD, whereas long-term PD survival is inferior or comparable to that of HD. Although it is an older report, the survival rate in US PD patients was 86.8% at 1 year and only 11.3% at 10 years [5]. In Korea, the survival rate in PD patients was 95.2% at 1 year and 36.4% at 10 years in the 2014 annual report of the Korean ESRD registry [6]; however, there have been some reports suggesting improvements in PD patient survival that

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must be considered when selecting dialysis modality.

Herein, we summarize recent global trends in PD patient survival. In addition, we aim to elucidate why patient survival is worse and cardiovascular events are more prevalent among PD patients than HD patients in Korea.

A global trend of improving PD patient survival

Recently, patient survival with PD as an initial treatment modality has consistently improved worldwide: this improvement was the most dramatic in the US. From patients starting dialysis in 2000 to those starting in 2008, survival rates improved in both HD and PD patients. Of note, the extent of improvement was more prominent in PD patients. The 5-year survival rate of HD patients improved from 34.5% to 40.2%, while that of PD patients greatly improved from 37.3% to 50.3% [1]. Therefore, the higher death rate of PD compared to HD seems to be at least comparable or reversed since the late 2000s. Most recently, US PD patients have had a similar life expectancy to that of HD patients [7]. The authors analyzed data from the US Renal Data System for secular trends in survival among patients treated with HD and PD on day 90 of ESRD in three 3-year cohorts (1996–1998, 1999–2001, and 2002–2004). Analysis revealed that there was a progressive attenuation in the higher risk of death in patients treated with PD in earlier cohorts. For the 2002–2004 cohort, there was no significant difference in risk of death between HD and PD patients.

A similar situation exists in Canada. The survival superiority of HD over PD was lost from an old cohort to a more recent one, with HD and PD showing equivalent outcomes [8]. This result was mainly associated with advancement in PD patient survival. The adjusted median life expectancy of HD and PD patients was 48.3 and 43.8 months in the 1991–1995 cohort period, respectively, while it was 51.7 and 50.8 months in the 2001–2004 cohort period.

In Australia and New Zealand, survival on dialysis therapy has also improved despite increasing prevalence of comorbid conditions [9]. Home HD has been widely used in these two countries, and the proportion of patients using home HD at the end of 2014 was 9% in Australia and 18% in New Zealand [10]. The survival rate was compared among in-center HD, home HD, and PD. Overall, there was a 25% lower adjusted mortality risk associated with dialysis inception during 2008 to 2012 compared to 1998

to 2002. In addition, there was a 21% reduction in mortality for those on facility HD therapy, a 27% reduction for those on PD therapy, and a 49% reduction for those on home HD therapy. Therefore, survival improvement has been more prominent in home-based dialysis therapy compared to facility HD.

A similar phenomenon is seen in Brazilian PD patients. A comparison of outcomes according to the era of dialysis initiation was performed in a nationwide PD cohort [11]. Although PD patients recently had more comorbidities including diabetes mellitus (DM), patient survival improved along all study periods. Compared to 2005/2006, patients starting in 2007/2008 had a relative risk reduction of 0.83, and those starting in 2009/2010 had a relative risk reduction of 0.69.

Although there has been no official report on temporal changes in patient survival including all European PD patients, there is scattered evidence in some countries. A cooperative study of Spanish PD registries showed that annual mortality was gradually decreasing, despite significant regional differences [12]. In addition, one report showed that Italian PD patient survival significantly improved over 30 years [13].

Recently, Hong Kong has experienced a situation distinct from that of global trends. The annual mortality rate of PD patients in 2000 was 26%, which was much lower in 2011 at 15% [14]. However, their 5-year patient survival was surprisingly found to be lower in the 2002–2006 cohort compared to the 1997–2001 cohort. The possible reasons include demographic differences between the two cohorts. Patients were older and the proportion of patients with diabetes or hypertension was also higher in the more recent cohort. Hong Kong is one of the most developed countries in terms of PD patient care; thus, the small change in patient characteristics could have significant effects on patient outcomes.

In almost all countries, patients starting PD have more unfavorable baseline characteristics, which may translate to worse survival; however, the survival rate of patients starting PD has gradually and significantly improved, likely due to advancements in standard PD patient care.

Comparison of PD patient survival between Korea and other countries

Ethnic diversity and the heterogeneity of patient char-

acteristics between those being treated with HD and PD at initiation of dialysis therapy are fundamental problems that make it difficult to draw conclusions regarding mortality. Although some cardiovascular morbidities such as myocardial infarction (MI) and congestive heart failure (CHF) are more prevalent in PD patients in Korea at the initiation of dialysis therapy, patients on PD are generally younger and have fewer comorbidities than those on HD [4]. In the US, PD patients are younger and healthier, whereas in Australia and New Zealand, PD patients are older and more commonly have diabetes, coronary artery disease (CAD), cerebrovascular accidents, and peripheral vascular disease [15]. On the contrary, in Taiwan, no definite differences were found in age, proportion of patients with diabetes and cardiovascular disease, and severity of illness as measured by the Charlson Comorbidity Index score between patients with HD and PD [16].

Differences in baseline characteristics are affected by various factors. First, patient-related factors such as lifestyle, economic status, predialysis education level, ability to perform self-care, and the availability of familial support are major determinants [17,18]. Social factors such as local cost barriers and reimbursement systems can also influence whether HD or PD is favored, which has a substantial impact on initial choice of modality [19,20]. Modality availability and physician preference also play considerable roles.

Despite these differences, several common points can be deduced from previous studies regarding mortality based on dialysis modality: (1) PD is associated with equivalent or better survival among non-DM patients and younger DM patients in the US, Canada, and Denmark; (2) the relative risk of death from PD versus HD varies with time on dialysis treatment—PD is usually associated with better survival during the first 1–2 years, and results vary thereafter; (3) in patients with cardiac comorbidities (CAD or CHF), the death risk of PD patients is higher than that of HD patients [2,21–23].

However, our analysis of nationwide data that included more than 32,000 patients suggested that these findings are not necessarily valid in Korea. After controlling for baseline differences in demographic data and comorbidities between HD and PD patients using propensity score matching (7,049 patients for each modality), PD use was associated with a 20% higher mortality than HD use when used as the first modality. The inferiority of

PD begins as early as 6 months after initiating dialysis therapy [4]. This trend was also evident in major cardiovascular outcomes in incident dialysis patients. Although hemorrhagic stroke was more frequently seen in HD than PD patients, the patients on PD had 29% and 18% higher risks of non-fatal MI and of the need for target vessel revascularization, respectively, than patients on HD [3].

Recent trends identified by inter-modality comparisons have indicated that, although PD use is declining, patient survival with PD as an initial modality has consistently improved in the US, Canada, and Europe and has become at least comparable or even superior to that of HD in recent years [7,8,24]. Korea is not an exception regarding recent improvements in PD-related outcomes.

In the Korean Society of Nephrology (KSN)-ESRD registry, there was significant improvement in long-term survival in both HD and PD patients. The five-year survival rate of HD patients improved from 52% in the 2005 report to 71% in the 2014 report, while that of PD patients greatly improved from 29% to 66% during the same period [6]. In addition, compared to patients initiating PD therapy during 1981–1992, those initiating therapy during 1992–2005 had 32% and 35% decreases in the risk of death and technique failure, respectively [25]. A similar trend was also observed in a more recent cohort in Korea: there was significant improvement in the survival rate of incident PD patients during a relatively short interval between 2005 and 2008 [26]. After adjusting for confounding variables, incident dialysis patients in 2008, including both HD and PD patients, had an 18% lower risk of death compared to those starting dialysis in 2005. This risk reduction was more prominent in PD patients than in HD patients.

Furthermore, it is likely that the survival rate of PD patients improved greatly after 2008 in Korea. Analysis of a prospective observational cohort of 31 Korean dialysis centers with patients who started dialysis from 2008 to 2011 revealed that the crude mortality rate was 78.5 per 1,000 patient-years, and patients on PD had a 51% lower risk of death compared to those on HD [27]. This is a significantly lower value compared with 116 per 1,000 patient-years in all Korean incident ESRD patients initiating dialysis from 2005 to 2008 [3]. Therefore, we assume that PD patient survival in Korea has dynamically improved recently.

Towards better PD patient survival in Korea

Although the exact reason why Korean PD patients have worse outcomes is not currently clear, there are some potential explanations. First, as mentioned above, two large-scale studies based on the database from the Center for Medicare and Medicaid Services (CMS) and the United States Renal Data System (USRDS) revealed that incident ESRD patients with preexisting CAD or CHF might not be optimal candidates for PD. Adjusted mortality risks were significantly higher in patients with CAD or CHF when initiating treatment with PD than with HD [21,22]. These findings directly opposed the widely accepted assumption that PD may have advantages over HD in cardiovascularly compromised patients in such a way that PD enables them to maintain more stable levels of blood pressure, volume status, electrolyte balance, and uremic toxins compared to HD [28–31]. In addition, other studies have also provided a basis to explain the disadvantage of PD in atherogenesis. Patients with PD had higher levels of total cholesterol, low-density lipoprotein-cholesterol, and lipoprotein(a) along with lower levels of high-density lipoprotein-cholesterol compared to those with HD [32]. Elevated levels of sympathetic activity and asymmetric dimethylarginine (ADMA), a potential inducer of endothelial dysfunction, were also reported in PD patients compared to those with HD [33]. Moreover, the chronic volume overload frequently encountered in PD patients may also create greater susceptibility to adverse cardiac remodeling than in HD patients [34].

We also found that previous history of MI or CHF has a significant interaction with dialysis modality for major adverse cardiac and cerebrovascular events (MACCE; defined as a composite endpoint of all-cause mortality,

non-fatal acute MI, percutaneous coronary intervention, coronary artery bypass graft, and non-fatal stroke) in Korean incident dialysis patients (Fig. 1). In brief, in patients with preexisting MI and CHF, PD conferred a 57% (relative risk [RR], 1.57; 95% confidence interval [CI], 1.20–2.05) and 25% higher (RR, 1.25; 95% CI, 1.10–1.42) risk, respectively, of MACCE than HD [3]. There is further evidence supporting this hypothesis: the proportion of patients with CHF was significantly lower in those starting PD in 2008 compared to those starting PD in 2005 (17.2% in 2005 vs. 13.6% in 2008, $P = 0.008$). This could be directly associated with improved patient survival among patients starting PD in 2008 compared to those starting in 2005.

Despite these evidence-based disadvantages of PD in cardiac-compromised patients, the practice pattern favoring PD over HD when choosing initial dialysis modality for such patients is still observed in Korea. According to our study [4], the proportions of patients with preexisting MI and CHF were significantly higher in PD patients than in HD patients (4.7% in PD vs. 3.3% in HD and 16.1% in PD vs. 14.3% in HD, respectively). Diabetes is another common condition associated with worse outcomes in patients on PD than in those on HD [2,23,35]. However, the percentage of diabetic patients was not significantly lower in patients initiating dialysis with PD than in those with HD.

Until 2008 in Korea, PD had been more frequently or at least comparably implemented in patients who were more likely to be adversely affected by PD than HD; this may lead to adverse outcomes from PD. This is in contrast to cases in Europe and the US where patients with CAD, CHF, and diabetes were at least evenly distributed between HD and PD or were more frequently assigned to

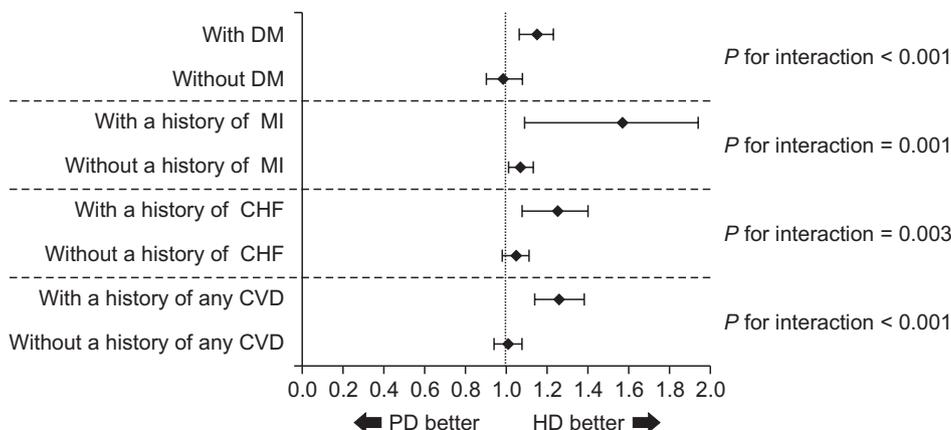


Figure 1. Comparison of adjusted relative risks of MACCE according to comorbidities. CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; HD, hemodialysis; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PD, peritoneal dialysis.

HD than to PD [36,37].

When mortality and cardiovascular morbidities were compared as a study endpoint, we adjusted for baseline cardiac conditions and diabetic status. However, this adjustment is not perfect. It is not possible to control for all factors underlying overt cardiac diseases and diabetes that are intrinsically involved in the progression of cardiovascular morbidities, which are the most important determinants of death in Korean dialysis patients [38]. Nevertheless, we do not think that all patients with CAD, CHF, or diabetes should avoid PD. Rather, we should identify baseline characteristics that do not increase risk or reduce risk and should refine them when those at high risk want to select PD as an initial dialysis modality.

Summary

A comparison of mortality and major cardiovascular events between HD and PD among dialysis patients in Korea revealed that PD was likely to be inferior to HD, with some exceptions in specific subgroups. However, this is not consistent with the results of other recent studies, and the results cannot be directly applied in practice. The discrepancy may be associated with differences in practice-patterns as well as ethnicity-related patient characteristics, potential selection bias from non-randomization, or other unmeasured factors [39]. With further analysis, we suggest that special attention should be given to patients with DM, CAD, or CHF when choosing PD as the first dialysis modality. In addition, more meticulous patient care should be offered during the entire duration of dialysis in high-risk PD patients in order to reduce mortality risk.

Recently, PD patient survival has significantly improved across countries around the world. However, their long-term survival has not yet reached a sufficient level. Further studies are required to investigate solutions for better PD patient survival.

Conflicts of interest

All authors have no conflicts of interest to declare.

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