Title
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Permalink
https://escholarship.org/uc/item/7kp5n67p

Journal
Seminars in nephrology, 31(2)

ISSN
0270-9295

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Publication Date
2011-03-01

DOI
10.1016/j.semnephrol.2011.01.004

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An Update on the Comparisons of Mortality Outcomes of Hemodialysis and Peritoneal Dialysis Patients

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Abstract

The number of dialysis patients continues to grow. In many parts of the world, peritoneal dialysis (PD) is a less expensive form of treatment. However, it has been questioned whether patients treated with PD can have as good a long-term outcome as that achieved with hemodialysis (HD). This skepticism has fueled ongoing comparisons of outcomes of patients treated with in-center HD and PD using data from national registries, or prospective cohort studies. There are major challenges in comparing outcomes with two therapies when the treatment assignment is non-random. Furthermore, many of the inter-modality comparisons include patients who started dialysis therapy in the 1990s. In many parts of the world, improvements in PD outcome have outpaced those seen with in-center HD. It is not surprising, then, that virtually all the recent observational studies from different parts of the world consistently show that long-term survival of HD and PD patients is remarkably similar. These studies support the case for a greater use of PD for the treatment of end-stage renal disease – this, in turn, could allow more patients to be treated for any given budgetary allocation to long-term dialysis.

Ever since the initial successful experience with continuous ambulatory peritoneal dialysis (PD), a large number of studies have tried to determine if the outcomes of PD patients are comparable to those achieved with hemodialysis (HD). A controlled clinical trial in which patients were randomly assigned to treatment with either PD or HD would be the best way to obtain unbiased estimates of the independent effects of dialysis modality on patient outcomes. However, the two dialysis modalities have disparate effects on patients’ daily lives. It is not surprising then that when patients are educated about their modality options, they often want to have a say in the choice and refuse to be randomized. The last attempt to conduct a randomized, controlled clinical trial was made under the auspices of the Netherlands Cooperative Study of Dialysis (NECOSAD). Only 38 (5%) of the 773 eligible subjects agreed to be randomized and hence, the study was substantially underpowered to allow any meaningful conclusions1. The most recent attempt is currently being undertaken...
in China – a pilot study has been successfully completed and the clinical trial is anticipated to begin enrollment in 2011 (ClinicalTrials.gov identifier: NCT00510549). However, the success and the results of this clinical trial will not be known for several years. Until then, one has to depend upon the results of observational studies that have attempted to compare the outcomes of patients treated with PD and HD.

**Inter-modality comparisons using Observational Studies: Challenges and Pitfalls**

The observational studies that have sought to compare the outcomes of PD and HD patients can be grouped into two broad categories – prospective, cohort studies and those that use data from national registries of dialysis patients. The major advantage of prospective cohort studies is that they contain detailed information about patient characteristics and hence allow for a more comprehensive adjustment for these differences. However, since such studies are expensive to undertake, the statistical power is limited since they include a relatively small number of subjects. On the other hand, national dialysis registries have substantially greater statistical power since they often include several thousand patients. However, such studies are limited by the paucity of medical information about each individual patient. There are no recent prospective, cohort studies that have compared the outcomes of PD and HD patients – both the CHOICE and NECOSAD studies in the United States and Netherlands respectively enrolled patients who began dialysis therapy in the 1990s. Thus, the only contemporary inter-modality comparisons are the ones that have used data from national registries of dialysis patients.

The inherent limitations of observational studies arise mainly out of substantial demographic, clinical, and psycho-social differences between patients treated with PD and HD. Experience in comparing the outcomes of PD and HD patients over the last two decades has led to clearer understanding of the challenges and pitfalls of such studies; some of these challenges and the potential solutions for study design are listed in Table 1. Indeed, studies that did not adequately address some of these challenges and pitfalls have produced results that are inconsistent and not reproducible.

Over the years, it has been appreciated that the relative risk of death for PD patients (as compared to those treated with HD) varies over their time on dialysis. Hence, it is best to study only incident patients and when reporting results, make a distinction between “early” and “late” outcomes. If only incident patients are used, the question that follows is - how should the initial dialysis modality be defined? Categorizing patients based on the dialysis modality on the first day of renal replacement therapy has several problems. First, HD is the initial dialysis modality for many new PD patients. This is often, though not always, a result of delayed referral to nephrologists. Second, in the United States, previously uninsured but Medicare-eligible in-center HD patients get insurance coverage from day 90 of end-stage renal disease. Consequently the administrative datasets are not as reliable for the first 90 days as they are thereafter. Finally, it is possible that many of the early deaths are secondary to the underlying co-existing illnesses, and since many of these patients are unable to perform home dialysis, they are treated with in-center HD. For all these reasons, dialysis modality on day 90 – with continuous treatment using that modality for 60 days (“60-day” rule) – is considered the initial dialysis modality.

The most vexing problem however, is the non-random assignment of patients to the two dialysis modalities. Including demographic, clinical, and laboratory-related variables as covariates in statistical models are probably not sufficient to account for the differences in patients who are treated with one dialysis modality compared to the other. Hence, propensity scores have increasingly been used to compare therapies when the assignment is non-random.
random\textsuperscript{15}. This score is the probability of each subject being treated with a given dialysis modality and is calculated using demographic, clinical, laboratory, and socio-economic data\textsuperscript{16}. Any two subjects, one treated with PD and the other with HD, with the same propensity score are deemed to be “randomly assigned” to their dialysis modality. Propensity scores can be used to match subjects, perform stratified analysis based upon quartiles or quintiles of such scores, or be used as covariates in survival analyses. Many recent inter-modality comparisons have used propensity scores – while these reduce bias, they don’t completely eliminate it\textsuperscript{2, 8, 9}.

In addition to interaction with time, relative outcomes of patients treated with different dialysis modalities vary depending on age, diabetic status, and presence/absence of co-existing illnesses\textsuperscript{17}. Hence, any sub-group analysis necessarily needs to account for these “interactions”. Finally, the reasons why patients reach the end of follow-up (censoring) may vary by dialysis modality. This, in turn, has the potential to influence survival comparisons. For example, the adjusted transplantation rate in the United States is about 50\% higher for patients treated with PD than with HD\textsuperscript{9}. Since only the healthiest patients undergo transplantation, this differential transplant rates has the potential to bias the results of comparison of outcomes of PD and HD patients. A greater efflux of healthier patients from the PD cohort may explain the loss of initial survival advantage seen in PD patients over longer-term follow-up\textsuperscript{13–14}. Conversely, longer transplant waiting times is likely to manifest as an improvement in survival – this may be one of many potential explanations for a greater improvement in outcomes of PD patients than has been observed for those treated with HD\textsuperscript{18}. Use of weights based upon the inverse probability of censoring because of transplantation can be used to minimize bias and have been incorporated in more recent analyses\textsuperscript{9, 19}.

Notwithstanding these advances in statistical analyses, even the most sophisticated statistical tools cannot definitively answer a key question – are any of the differences in survival seen in such registry-based comparisons attributable to the dialysis modality or to differences in patients who chose a given dialysis modality? It is with this caveat that one should examine the current body of literature in this field.

**Contemporary Inter-Modality Comparisons**

Starting from the early 1980s, a large number of studies have compared the survival of patients treated with PD and HD. Over the last three decades, the study design has evolved from single-center and multi-center studies in the 1980s and early 1990s, to either prospective cohort studies or those using data from national registries of dialysis patients thereafter. The early studies produced inconsistent results – it was largely through attempts to explain these inconsistencies that have led to our current understanding of challenges and pitfalls when comparing survival of PD and HD patients (as reviewed in the preceding section). Indeed, registry-based studies from Canada, United States, and Denmark that included patients that began renal replacement therapy in the 1990s took care to avoid the common pitfalls, and came to remarkably similar conclusions (reviewed previously\textsuperscript{20}). These studies consistently showed a lower risk for death for PD patients early during the course of end-stage renal disease (1–3 years, depending on the country)\textsuperscript{13–14, 17–21}. Over time, this “survival advantage” dissipated and, particularly in the United States, the long-term mortality risk for PD patients was higher than that for those treated with HD. Furthermore, this modality risk-relationship was modified by three important variables – age, diabetic status, and presence/absence of co-existing illnesses\textsuperscript{17}. Thus, the better the overall health of a patient, the greater and longer was the survival advantage for PD patients. Conversely, the poorer the overall health of a patient, the lesser and shorter was the survival advantage with PD\textsuperscript{22}. Thus, most studies indicated a robust short- and long-term survival
advantage with PD for non-diabetics with no other co-morbidity; older diabetics had a demonstrably worse long-term outcome, particularly in studies from the United States. Notwithstanding these consistent observations, it has been difficult to conclude whether these differences are attributable to the dialysis modality.

However, the practice of both PD and HD has changed considerably from what it was in the early 1990s. Starting from the mid-1990s, the survival of patients treated with both dialysis modalities has improved, albeit at different rates. Much greater gains have been made in the outcomes of PD patients than have been made in those of HD patients. This is particularly true for the survival of patients in the first 12 months of treatment – while the first-year mortality of PD patients has decreased significantly since the mid-1990s, there have been no significant changes in the first year mortality of HD patients. Similar trends with greater improvements in outcomes of PD patients have been reported by investigators from Canada, Denmark, and Spain at international meetings – however, findings from these countries have not been published to date. These considerations make a strong argument against using the survival data of patients who began dialysis in the 1990s to make clinical decisions today. Studies that are based, at least in part, on patients who started dialysis after 2000 are summarized in Table 2. As is apparent, they span countries from Europe (Netherlands), Asia (Taiwan), South America (Colombia), Oceania (Australia and New Zealand), and North America (United States). The conclusions of these studies from different parts of the world is again remarkably consistent – if the analyses are restricted to patients who started dialysis in the 2000s, there is no difference in the survival (for up to 4-5 years) of patients who begin treatment with either PD or HD. In the United States, the adjusted 5-year survival of PD and HD patients who started dialysis in 2002-04 was 33% and 35% respectively, and the median life-expectancy was 37 and 38 months respectively.

Consistent with these findings, another study demonstrated that the adjusted four-year survival of PD and HD patients who started dialysis in 2003 in the United States was 47% and 48% respectively. The trends in sub-groups are the same as had been reported for patients who were treated in the 1990s. However, the survival advantage of younger, non-diabetics has become greater and the higher risk among older diabetics treated with PD has lessened compared to those treated with HD. At this time, there is limited evidence to determine why the outcomes of PD patients have improved more than that of those treated with HD. Some possible explanations for the differential improvement in outcomes are summarized in Table 3. Greater attention to PD prescription and reduction in infectious complications are the two leading explanations for the improvement in survival of PD patients. The former includes a greater use of automated PD. While two large registry studies have demonstrated that both continuous ambulatory and automated PD provide similar outcomes overall, rapid transporters treated with automated PD have a better survival than with continuous ambulatory PD. A selective movement of rapid transporters to automated PD could have contributed to the improvement in outcomes of the remaining patients treated with continuous ambulatory PD and this, in turn, could have contributed to the overall improvement in outcomes of PD patients.

Conclusions

Contemporary studies suggest that the effect of dialysis modality on patient survival is rather small, if any. It follows then that survival studies should not be used in making decisions about the appropriate dialysis modality for an individual patient. This should, instead, be based upon a discussion about patients’ expectations about their life-style, which in turn can only be made after early and iterative dialysis modality education. Studies suggest that most patients starting dialysis in United States are often unaware of alternatives to in-center HD, and a randomized controlled trial indicates that comprehensive modality education...
increases selection of self-care dialysis\textsuperscript{28, 29}. Hence, comprehensive dialysis modality education is likely to expand the use of PD. It is important to note that the improvement in PD outcomes and the consequent similarity in long-term outcomes of patients treated with PD and HD has been reported from countries with a wide range of PD uptake – from as low as 6-7\% in the United States to almost 50\% in Colombia. These studies support the case for greater use of PD in the treatment of end-stage renal disease – this, in turn, could allow more patients to be treated for any given budgetary allocation to long-term dialysis.

Acknowledgments

Acknowledgements and Conflicts of Interest

This work is supported, in part, by grant DK077341 from the National Institutes of Health (RM and KKZ), Baxter Health Care (RM), and DaVita Inc. (RM and KKZ).

Rajnish Mehrotra has received research grants, served as ad hoc consultant, and honoraria from Baxter Health Care. Rajnish Mehrotra and Kamyar Kalantar-Zadeh have received research grants from DaVita Inc.

Reference


Table 1
Pitfalls and challenges and proposed solutions when performing studies comparing the outcomes of end-stage renal disease patients treated with hemodialysis or peritoneal dialysis

<table>
<thead>
<tr>
<th>Pitfalls/Challenges</th>
<th>Potential Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in relative risk over time (time-interaction)</td>
<td>Include incident patients or those of recent vintage; break down results for different follow-up periods</td>
</tr>
<tr>
<td>Definition of initial dialysis modality – make allowances for modality switches in the first 90-120 days of end-stage renal disease</td>
<td>Modality on day 90 and continuous treatment with the modality for at least 60 days. The use of day 90 is dictated, in part, by administrative reasons in the United States, and hence is arbitrary. On the other hand, defining modality on the first day of renal replacement therapy has the potential to introduce bias in favor of PD - it will exclude patients who are referred late and start PD after a variable period of treatment with HD.</td>
</tr>
<tr>
<td>Selection of dialysis modalities is non-random</td>
<td>Calculate propensity scores that numerically describe the probability for a patient to be treated with a given dialysis modality based upon known patient characteristics; outcomes can be analyzed in sub-groups based upon propensity scores or included as a covariate (directly or its inverse) in statistical models</td>
</tr>
<tr>
<td>Intent-to-treat or as-treated analysis</td>
<td>Perform both and interpret clearly</td>
</tr>
<tr>
<td>For as-treated analysis, how should deaths after change in dialysis modality be handled?</td>
<td>Allow a grace period (generally 60 days) such that deaths that occur within that period are assigned to the previous dialysis modality</td>
</tr>
<tr>
<td>Sub-group analyses and statistical interactions</td>
<td>Several studies have shown statistically significant interactions with age, diabetic status, and presence/absence of co-morbidity. Present results after stratifying the study population into sub-groups based on these variables.</td>
</tr>
<tr>
<td>Problem of over-adjustment – including variables that may mediate the pathways of higher (or lower) risk with different dialysis modalities</td>
<td>Exercise care in including variables in models that may mediate the higher (or lower) risk with each dialysis modality. For example, higher CRP levels in HD patients may be a result of the use of venous catheter – which may, in turn, mediate the higher risk seen early with HD. Alternatively, lower serum albumin is a consequence of PD itself (secondary to peritoneal albumin loss) and inclusion of values obtained after start of dialysis may bias results in favor of PD.</td>
</tr>
<tr>
<td>Residual Confounding – inability to adjust for unknown factors that may differentially affect the comparison of outcomes</td>
<td>None</td>
</tr>
<tr>
<td>Transplantation rates of patients treated with different dialysis modalities</td>
<td>Only the healthiest patients undergo renal transplantation and if transplantation rates vary by dialysis modality, it may bias results against the modality with higher transplantation rates (by removing the healthiest patients from the cohort at a faster rate). Use weights that account for the probability of being censored for transplantation</td>
</tr>
</tbody>
</table>
Table 2

Studies comparing the mortality outcomes of incident hemodialysis and peritoneal dialysis patients that included patients who started treatment on or after 2000

<table>
<thead>
<tr>
<th>First Author (publication year)</th>
<th>Cohort period/ Country</th>
<th>Secular Trends</th>
<th>Inclusion criteria/ Sample size</th>
<th>Data Adjusted for</th>
<th>Follow-up duration</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liem 4 (2007)</td>
<td>1987-2002 Netherlands</td>
<td>No</td>
<td>16,643 (HD 10,841; PD 5,802)</td>
<td>Age, gender, renal diagnosis, year of first RRT, and dialysis center</td>
<td>Up to 16 years</td>
<td>In younger diabetic and non-diabetic patients, lower risk for PD patients for the first 15 months; no difference thereafter. In older non-diabetics, lower risk for PD patients in the first 6 months, but higher risk after the first 15 months. In older diabetics, no difference in early death but higher risk for PD patients after the first 15 months.</td>
</tr>
<tr>
<td>Huang 5 (2008)</td>
<td>1995-2002 Taiwan</td>
<td>No</td>
<td>48,629 (HD 45,820; PD 2,809)</td>
<td>Age, gender, selected co-morbidity and diabetic status</td>
<td>Up to 6 years</td>
<td>Overall similar 5-year (HD, 54%; PD, 56%) and 10-year survival (HD, 34%; PD, 35%); sub-group analysis showed higher risk for death among all diabetics, and older non-diabetics (&gt; 55 years age)</td>
</tr>
<tr>
<td>Sanabria 6 (2008)</td>
<td>2001-2003 Colombia</td>
<td>No</td>
<td>923 (HD 437; PD 486)</td>
<td>Age, gender, socio-economic status, education, medical insurance, SGA score, selected co-morbidity, and laboratory variables, cause of ESRD</td>
<td>Up to Dec 2005</td>
<td>No difference in overall adjusted mortality rates between HD and PD; lower death risk for young, non-diabetic patients treated with PD but similar outcomes in all other groups</td>
</tr>
<tr>
<td>McDonald 7 (2009)</td>
<td>1991-2005 Australia and New Zealand</td>
<td>Yes</td>
<td>25,287 (HD 14,733; PD 10,554)</td>
<td>Age, Gender, BMI, race and selected co-morbidity, and propensity scores</td>
<td>Up to 12/31/05</td>
<td>Overall 11% lower risk for death for PD patients in the first year, but 33% higher risk after the first 12 months; early survival advantage with PD seen only in young patients without co-morbidities. In the most recent cohort (2004), no difference in long-term mortality of HD and PD patients</td>
</tr>
<tr>
<td>Weinhandl 8 (2010)</td>
<td>2003 USA</td>
<td>No</td>
<td>6337 pairs (HD 3,637; PD 6,337)</td>
<td>Age, Gender, race and selected co-morbidity, and propensity scores</td>
<td>Up to 4 years</td>
<td>Overall mortality risk was 8% lower for PD patients. Similar adjusted four-year survival (HD, 48%; PD, 47%)</td>
</tr>
<tr>
<td>Mehrotra 9 (2010)</td>
<td>1996-2004 USA</td>
<td>Yes</td>
<td>684,426 (HD 620,020; PD 64,406)</td>
<td>Age, Gender, race and selected co-morbidity and propensity scores</td>
<td>Up to 5 years</td>
<td>No significant difference in the five-year adjusted survival of HD and PD patients (35% and 33% respectively). Lower risk for death for younger, non-diabetic PD patients; higher death risk for older diabetics – particularly those with additional co-morbidity – treated with PD</td>
</tr>
</tbody>
</table>

HD – hemodialysis; PD – peritoneal dialysis; RRT – renal replacement therapy
Possible explanations for the differential improvement in outcomes of patients treated with hemodialysis and peritoneal dialysis in the United States

<table>
<thead>
<tr>
<th>Related To Dialysis Practices</th>
<th>Unmeasured confounding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD Related</strong></td>
<td></td>
</tr>
<tr>
<td>Better and individualized PD prescription management over the years</td>
<td>Residual confounding as patients starting PD are younger and healthier than in previous years</td>
</tr>
<tr>
<td>Reduced risk of infectious complications</td>
<td>Longer waiting times for transplantation – healthier patients remain dialysis-dependent for longer periods of time. Since PD patients have higher transplantation rates, outcomes of this cohort are more likely to be affected.</td>
</tr>
<tr>
<td>More widespread use of quality improvement programs</td>
<td></td>
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<tr>
<td>More attention to maintenance of normal volume status</td>
<td></td>
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<tr>
<td><strong>HD Related</strong></td>
<td></td>
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<tr>
<td>Greater and longer use of tunneled venous catheters</td>
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</tbody>
</table>