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Sudden and cardiac death rates in hemodialysis patients

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Background. Sudden and cardiac death (including death from congestive heart failure, myocardial infarction, and sudden death) are common occurrences in hemodialysis patients. The intermittent nature of hemodialysis may lead to an uneven distribution of sudden and cardiac death throughout the week. The purpose of this study was to assess the septadian rhythm of sudden and cardiac death in hemodialysis patients.

Methods. Data from the United States Renal Data System (USRDS) were obtained to examine the day of death for United States hemodialysis and peritoneal dialysis patients from 1977 through 1997. The days of death were also determined for patients in the Case Mix Adequacy Study of the USRDS.

Results. There was an even distribution of sudden and cardiac deaths for patients on peritoneal dialysis, and hemodialysis patients dying of noncardiac deaths also had an even distribution. For all hemodialysis patients, Monday and Tuesday were the most common days of sudden and cardiac death. For patients in the Case Mix Adequacy Study designated as Monday, Wednesday, and Friday dialysis patients, 20.8% of sudden deaths occurred on Monday compared with the 14.3% expected ($P = 0.002$). Similarly, 20.2% of cardiac deaths occurred on Monday compared with the 14.3% expected ($P = 0.0005$). Similar trends were found on Tuesday for Tuesday, Thursday, and Saturday dialysis patients.

Conclusions. The intermittent nature of hemodialysis may contribute to an increased sudden and cardiac death rate on Monday and Tuesday for patients enrolled in the USRDS.

The poor survival of U.S. dialysis patients has been well characterized. A white, male patient between 55 and 59 years of age receiving dialysis between 1991 and 1993 had an expected remaining lifetime of 4.0 years, compared with an average expected remaining lifetime of 22.4 years for a similar person not requiring dialysis [1]. The increased mortality rates are also present in women and African American dialysis patients. According to data from the United States Renal Data System (USRDS), approximately 42% of dialysis patient deaths are recorded as cardiovascular in origin, with 22.4% of deaths related to cardiac arrest or arrhythmia [2]. A better understanding of the immediate cause of death could be helpful in decreasing death rates from cardiac arrest, as well as overall mortality rates.

Hemodialysis (HD) patients are at an increased risk of sudden death for many reasons. A large proportion of these patients suffer from coronary artery disease [3] and cardiomyopathy [4], well-known risk factors for sudden death [5]. In addition, these patients have unique problems that put them at high risk. Volume overload and metabolic abnormalities such as hyperkalemia affect cardiac function and may lead to sudden death. Although peritoneal dialysis (PD) patients dialyze continuously and maintain a relatively stable volume and electrolyte status, HD patients have large swings in volume status and serum potassium because of the intermittent nature of dialysis. These swings are especially prominent over the HD weekend interval when patients have three days, rather than the customary two days, without dialysis. During this interval, patients may gain up to 7 kg.

We hypothesized that the intermittent nature of HD contributes acutely to an increased risk of sudden death and possibly death from all cardiac causes. We postulated that HD patients receiving treatment on Monday, Wednesday, and Friday (MWF) would be more likely to die on Monday; and Tuesday, Thursday, and Saturday (TTS) dialysis patients would be more likely to die on Tuesday. This increased death rate would be due to the increased volume and potassium accumulated over the longer weekend interval, as well as the development of postdialysis hypotension from the removal of large amounts of fluid.

METHODS

The data used in this analysis were obtained from the USRDS [6]. The standard analysis files provided information regarding the date of death, cause of death, place of death, and dialysis modality for the entire dialysis population from 1977 through 1997. The preceding

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information was available on 375,482 deaths during this time period, with 326,728 deaths in HD patients and 48,754 deaths in PD patients. In addition, information was obtained from the USRDS Case Mix Adequacy Study (CMAS). In this study of 7096 HD patients (6749 with complete data), predialysis and postdialysis blood urea nitrogen measurements were performed at the initiation of the study and monthly for a six-month period. Information on comorbid conditions and compliance with dialysis were also collected. Follow-up information was obtained from the standard USRDS data files, which contain the date and cause of death. There were 4378 deaths during the follow-up period.

In the entire USRDS cohort, 49,961 (13.3%) of deaths were reported as occurring on the last day of the month, and in the CMAS, 612 (14%) deaths were reported as occurring on the last day of the month. The increased death rate on the last day of the month was noted throughout the entire time period, indicating that the last day of the month was used as the default date when the exact date of death was not known. For this reason, patients whose death date was listed as the last date of the month were excluded because the exact date of death (and therefore the exact day of the week) could not be determined and was vital for this study. Because the last date of the month was randomly distributed throughout the study, including or excluding patients who died on the last day of the month had little effect on the day of the week distribution for deaths.

The cause of death was obtained from the Health Care Finances Administration End Stage Renal Disease Death Notification Form. The patient's nephrologist or allied health care personnel were responsible for categorizing the cause of death. Possible categories included cardiac arrest cause unknown, cardiac arrhythmia, myocardial infarction, congestive heart failure, and pericarditis. For this study, deaths were then placed into the following categories: (*a*) Sudden death was considered to occur if the cause of death was listed as cardiac arrest cause unknown or cardiac arrhythmia. (*b*) A cardiac death was considered to occur if the cause of death was one of the following: cardiac arrest cause unknown, cardiac arrhythmia, myocardial infarction, cardiac death (other than pericarditis), atherosclerotic heart disease, cardiomyopathy, valvular heart disease, and pulmonary edema caused by exogenous fluid. (*c*) A control group was formed in which the cause of death was one of the following: malignancy, gastrointestinal hemorrhage, septicemia, perforation of peptic ulcer, perforation of bowel, pulmonary infection, AIDS, tuberculosis, or other infection. The day of the week distribution for death was determined for the entire USRDS population and was determined separately for PD and HD patients. Excluding patients whose death date was the last day of the month, there were 283,015 HD patient deaths. Of these deaths, 128,861 were classified as cardiac death, 45,940 as sudden death, and 42,538 as control deaths. Of 42,506 PD patient deaths, 19,752 were classified as cardiac death, 6755 as sudden death, and 7216 as control deaths. To test if there was an increased risk of death on a given day of the week, a binomial test was performed to see if the observed proportion of deaths was higher than the expected proportion of deaths (1 out of 7 or 14.3%).

For the CMAS, patients were considered to be MWF dialysis patients if there were at least three laboratory measurements and the last three (consecutive) measurements occurred exclusively on a MWF. Patients were designated as TTS patients in a similar manner. For each death category, the proportion of deaths occurring on each day of the week was calculated for MWF and TTS patients. To test if there was an increased risk of death on Monday for MWF patients and Tuesday for TTS patients, a binomial test was performed to see if the observed proportion of deaths was higher than the expected proportion of deaths (1 out of 7 or 14.3%). In the CMAS, the following characteristics were compared between patients dying of sudden death and patients dying of all other causes: age, gender, race, serum albumin, history of coronary artery disease, prior myocardial infarction, congestive heart failure, atrial fibrillation, amputation caused by peripheral vascular disease, and diabetes mellitus. In addition, the mean weight removed during several dialysis treatments, the number of treatments shortened by 10 or more minutes in January 1991, and the number of skipped treatments in January 1991, were compared.

In the CMAS study, there were 6137 patients who had complete data and did not die on the last day of the month. There were 4378 patient deaths in this group. Of the patients, 1588 could be classified as MWF HD patients, of whom 565 were classified as cardiac death, 395 as sudden death, and 278 as control deaths. Similarly, 1077 patients could be classified as TTS HD patients, of whom 395 were classified as cardiac death, 276 as sudden death, and 183 as control deaths.

In order to study whether patients with increased age, coronary artery disease, diabetes mellitus, and/or congestive heart failure were more likely to suffer a cardiac death on the first day of the week (Monday for MWF HD patients and Tuesday for TTS HD patients), a logistic regression model was created. The outcome variable was cardiac death on the first day of the dialysis week versus cardiac death on any other day of the dialysis week. The presence of congestive heart failure, diabetes mellitus, coronary artery disease, and age were entered in a univariate logistic model.

The following approach was used to calculate the excess death rate due to the increase in Monday and Tuesday deaths. First, the difference between the expected and observed cardiac death events on Monday were cal-

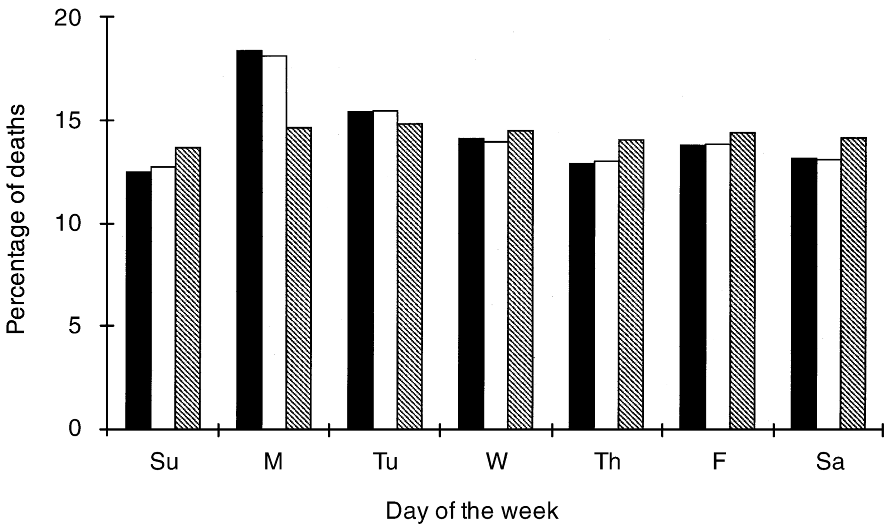

Fig. 1. Distribution of deaths according to day of the week for hemodialysis patients. Symbols are: (■) cardiac arrest; (□) all cardiac; (▨) control.

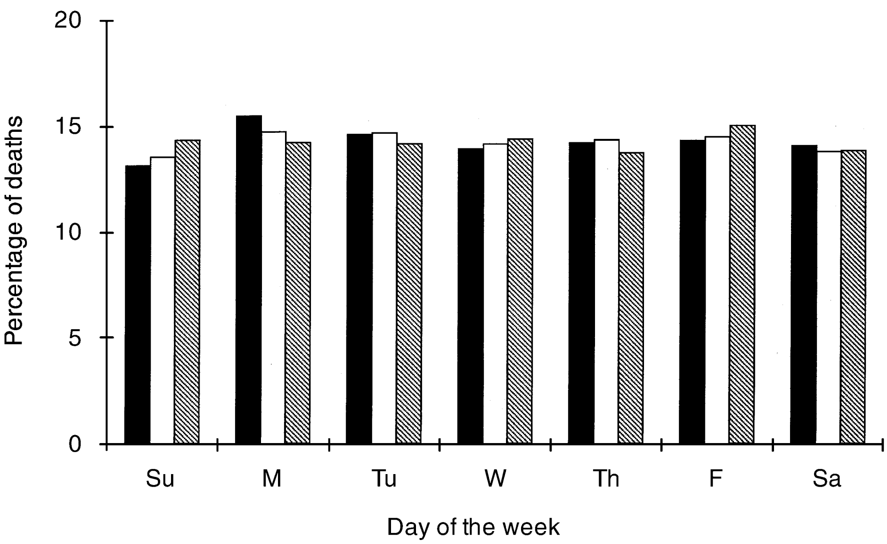

Fig. 2. Distribution of deaths according to day of the week for peritoneal dialysis patients. Symbols are: (■) cardiac arrest; (□) all cardiac; (▨) control.

culated for the CMAS. This number of deaths was then divided by the total number of cardiac deaths in the CMAS to obtain the proportion of cardiac deaths associated with the increase in cardiac death rate on Monday. This proportion was then multiplied by the annual cardiac death rate for the years 1994, 1995, and 1996 to obtain the number of deaths per year, which might be related to this increased cardiac death rate.

RESULTS

Figure 1 shows the distribution of sudden death, all cardiac death, and control deaths by day of the week for all HD patients in the USRDS. It is important to note that this figure includes patients who received treatment on MWF, as well as those who received treatment on TTS, as there was no way to determine which patients received dialysis on MWF and which patients received dialysis on TTS. There is a markedly increased risk of sudden death (18.4 vs. 14.3% expected, $P < 0.00001$) and cardiac death (18.1 vs. 14.3% expected, $P < 0.00001$) on Monday. In contrast, the death rate for controls on Monday is 14.6% (vs. 14.3% expected, $P = 0.058$), and the death rate for control deaths is quite steady for each day of the week. The next most common day of cardiac and sudden death is Tuesday, on which 15.4% of cardiac deaths and 15.4% of sudden deaths occur ($P < 0.00001$ for each). For all other days of the week, cardiac and sudden death rates are less than the 14.3% expected. In comparison, the control death rate ranges from 13.7 to 14.8% throughout the week.

Figure 2 shows the distribution of sudden death, all

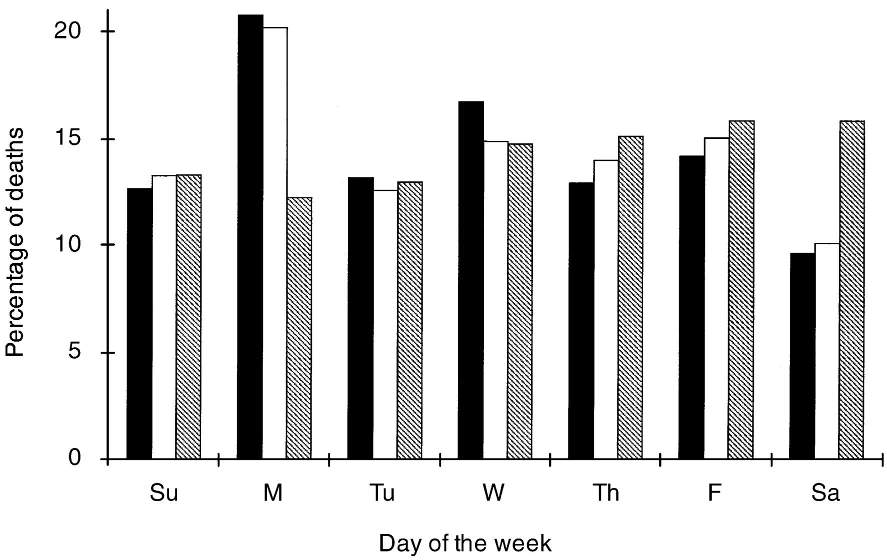

Fig. 3. Distribution of deaths according to day of the week for Monday, Wednesday, and Friday hemodialysis patients. Symbols are: (■) cardiac arrest; (□) all cardiac; (▧) control.

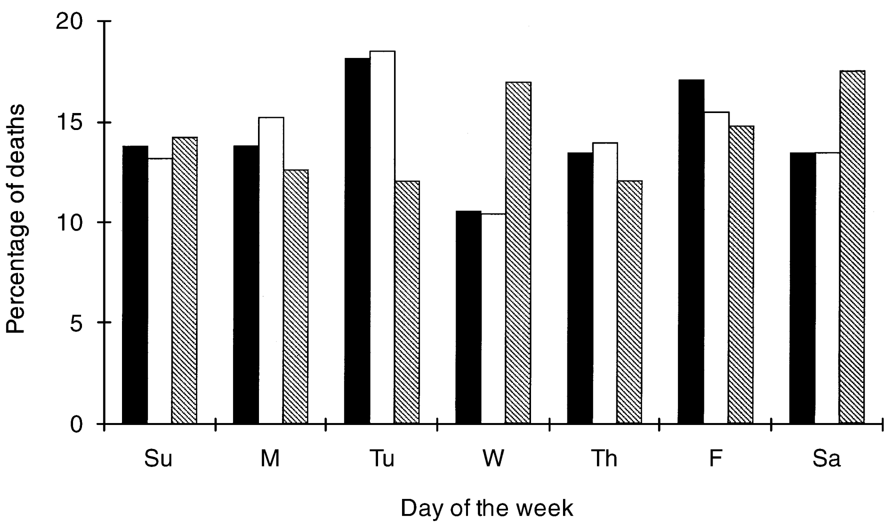

Fig. 4. Distribution of deaths according to day of the week for Tuesday, Thursday, and Saturday hemodialysis patients. Symbols are: (■) cardiac arrest; (□) all cardiac; (▧) control.

cardiac death, and control deaths by day of the week for all PD patients in the USRDS. The percentage of patients experiencing cardiac death on Monday was 14.8 versus the 14.3% expected ($P = 0.055$), and the percentage experiencing sudden death on Monday was 15.5 versus the 14.3% expected ($P = 0.005$). The difference in the percentage of patients suffering sudden death on Monday and the expected is small and reaches significance because of the very large size of the database. The proportion of deaths for sudden death, all cardiac deaths, and control deaths stayed quite stable throughout the week, ranging from 13.2 to 15.5% for sudden death, from 13.6 to 14.8% for all cardiac death, and from 13.9 to 15.1% for control deaths.

Figure 3 shows the distribution of sudden death, all cardiac death, and control deaths by day of the week for MWF HD patients in the CMAS. Monday had a much higher rate of sudden death (20.8 vs. 14.3% expected, $P = 0.002$) and all cardiac death (20.2 vs. 14.3% expected, $P = 0.0005$). In contrast, the proportion of control deaths remained relatively stable throughout the week, with more occurring toward the end of the week. Wednesday and Friday—the two other dialysis days—had the second and third highest rates of cardiac death (15.0 and 14.9%). Figure 4 shows the distribution of sudden death, all cardiac death, and control deaths by day of the week for TTS HD patients. Trends were not as strong in this group of patients as in the MWF HD patients. There was a statistically increased proportion of all cardiac deaths on Tuesday (18.5 vs. 14.3%, $P = 0.03$), but the increased proportion of sudden death on Tuesday was not statistically significant (18.1 vs. 14.3%, $P = 0.10$).

Table 1. Comparison of characteristics between patients who experienced sudden death and those patients who did not in the CMAS

Characteristic	Sudden death	Other patients	*P* value[b]
Age *years*[a]	60.4 ± 14.6	60.5 ± 14.9	0.82
Gender % *male*	51.0	50.8	0.91
Race % *white*	60.5	63.6	0.13
Serum albumin *g/dl*[a]	3.65 ± 0.49	3.71 ± 0.52	< 0.001
Coronary artery disease %	52.7	38.8	< 0.001
Prior myocardial infarction %	21.1	14.6	< 0.001
Congestive heart failure %	59.1	44.0	< 0.001
Atrial fibrillation %	16.3	10.9	< 0.001
Amputation due to peripheral vascular disease %	11.0	7.4	0.001
Diabetes %	48.2	37.6	< 0.001
Weight loss during dialysis *kg*[a]	3.34 ± 1.35	3.34 ± 1.32	0.91
Number of shortened treatments[a]	1.00 ± 2.10	0.99 ± 2.20	0.90
Number of skipped treatments[a]	0.61 ± 1.54	0.57 ± 1.46	0.65

[a] Values represent mean ± standard deviation
[b] T test for continuous variables and Chi-squared test for discrete variables

Table 1 is a comparison of baseline characteristics for CMAS patients who died of sudden death and those patients who did not. Patients who died of sudden death were more likely to have coronary artery disease and peripheral vascular disease. They were not more likely to skip dialysis treatment or have increased weight removal with dialysis treatments.

Univariate logistical regression models were then created to determine if the presence of coronary artery disease, congestive heart failure, diabetes mellitus, increasing age, or the amount of weight removed at a dialysis treatment were associated with an increased risk of death on the first day of the dialysis week. None of the preceding variables were found to be associated with an increased risk of death on Monday for MWF HD patients or Tuesday for TTS HD patients.

In the CMAS, there were 177 cardiac deaths occurring on Monday and 703 cardiac deaths during the rest of the week, or an average of 117 deaths per day. Therefore, there were 60 extra deaths on Monday or an excess death rate of 6.82%. Applying this percentage to the number of cardiac deaths in 1994 (13,732), 1995 (13,936), and 1996 (16,317), there would be an excess of 936, 950, and 1112 deaths for each year.

DISCUSSION

Unlike continuous ambulatory PD and renal transplantation, HD is an intermittent therapy that results in the periodic accumulation and removal of toxins, electrolytes, and fluid. These fluctuations are especially prominent over the weekend interval when the three-day dialysis-free interval, together with increased social activities, results in large interdialytic weight gains noted by all clinical nephrologists on Monday and Tuesday. We hypothesized that these changes would lead to an increased cardiac and sudden death rate on Monday for MWF HD patients and Tuesday for TTS patients.

The results from the entire USRDS database indicated a nonrandom distribution of cardiac deaths for HD patients. Figures 1 and 2 demonstrate that although cardiac and noncardiac deaths for PD patients are rather evenly distributed throughout the week, cardiac deaths in HD patients occur most frequently on Monday, with the next most common day of death being Tuesday. In addition, noncardiac deaths for HD patients are evenly distributed throughout the week.

Data from the CMAS were then used to identify the most likely dialysis schedule. MWF HD patients were much more likely to die a cardiac death on Monday than other days of the week. Wednesday and Friday—the other dialysis days—were the next most common days of cardiac death. Deaths from noncardiac causes were evenly distributed. Patients on a TTS dialysis schedule were more likely to die from a cardiac cause on Tuesday than other days, although these changes were not as prominent.

Taken together, these results show an increased risk of cardiac and sudden death on Monday for MWF HD patients and Tuesday for TTS HD patients. There are likely many factors contributing to this increased death rate. Large weight gains or increases in serum potassium may cause volume overload or hyperkalemia resulting in death. These metabolic imbalances are especially deleterious for patients with dilated cardiomyopathy, underlying cardiac arrhythmias, or coronary artery disease. These groups of patients were found have an especially increased risk of sudden death in this study. Patients who survive until their dialysis treatment on Monday or Tuesday then undergo the removal of very large amounts of fluid, frequently resulting in postdialysis hypotension. Such hypotension may have disastrous consequences in patients with underlying coronary artery disease and cardiac hypertrophy, conditions especially common in the dialysis population [3, 7]. Both predialysis hypertension and postdialysis hypotension have been found to be risk factors for mortality in HD patients [8]. In this study, the time of death was not known, so we were unable to ascertain how many deaths occurred prior to or following a dialysis treatment. In a previous study, we found that sudden death occurs most frequently immediately before or after a dialysis treatment, with an equal distribution of deaths before and after treatment (abstract; *J Am Soc Nephrol* 8:210A, 1997).

Studies in other populations have inconsistently noted an increased sudden death rate and an increased rate of myocardial infarction on Mondays. In a study of 2999 patients admitted to the hospital with myocardial infarction, Muller et al did not find a weekly rhythm in the onset of infarction [9]. Willich et al found that sudden cardiac death was evenly distributed throughout the week in 2960 patients and that myocardial infarction was increased by 33% on Monday in 884 patients who worked, whereas there was a more even weekly distribution in nonworking patients [10]. In the Framingham Heart Study, sudden death was found to be evenly distributed throughout the week [11]. The GISSI 2 Study noted a 10% increase in myocardial infarction on Mondays [12].

The increased cardiac and sudden death rate was more prominent on Mondays for MWF HD patients than Tuesdays for TTS patients. There are several possible explanations for this observation: (*a*) The exact date of dialysis was not known, and a surrogate for the dialysis schedule (the day of the last three determinations of adequacy in the CMAS) was used. Patients generally prefer a MWF dialysis schedule, and those who start on a TTS schedule are often placed on a waiting list for a MWF appointment. In addition, some units are only open on MWF. Therefore, MWF is more likely to be correctly identified as the dialysis day. Misclassification of the patients to the wrong day is likely to underestimate the magnitude of deaths occurring on Monday for MWF dialysis patients and Tuesday for TTS patients. (*b*) Patients who dialyze on a TTS schedule have a dialysis treatment after the first weekend night (Friday), and they may, therefore, have less fluid and electrolyte accumulation. In addition, if TTS patients note that they are volume overloaded, they can request dialysis on Monday, whereas MWF patients do not have this alternative. (*c*) Sudden and cardiac death may be more common in the general population on Mondays, and this effect may partially carry over into the dialysis population.

As one might expect, patients with coronary artery disease, diabetes mellitus, and congestive heart failure were more likely to suffer a sudden death than patients without these conditions. However, these patients did not have an increased likelihood of cardiac death on the first day of the dialysis week; the increased risk of cardiac death in this group was present throughout the week.

A shortcoming of this study was that a rigorous definition of sudden death (or deaths of other cardiac causes) was not used. Further investigations that employ a standard definition of sudden death are needed.

Either random or systematic bias could affect the results of this study. Random bias would occur if dates of death were entered incorrectly on a random basis. This would decrease the ability of the study to find higher proportions of cardiac death on Monday or Tuesday. In a validation study of the USRDS, the date of death was in exact agreement with medical records in 80.5% of cases [13]. We noted the last day of the month listed as the date of death for 13%. It is likely that this error accounted for the majority of cases where the date of death was incorrect. Systematic bias could also affect the results of the study. The finding that cardiac deaths in PD patients and control deaths in HD patients are evenly distributed rules out many possible sources of systematic bias.

The estimate of the increased death rate of 1000 deaths per year, which may be related to intermittent dialysis, is quite conservative and takes into account only the immediate death rate on Monday or Tuesday. Longitudinal risks from intermittent dialysis, including the development of cardiac hypertrophy and hypertension from intermittent volume gains and central nervous system effects from alternating hypotension and hypertension, are likely to contribute to an increased death rate as well.

What should be done to prevent the increased rate of sudden and cardiac death on Monday or Tuesday in HD patients? It is extremely important to educate patients about the immediate effects of increased fluid and electrolyte intake, especially over the weekend. It is especially important to target patients with coronary artery disease and congestive heart failure. In addition, it is becoming increasingly evident that the short, intermittent nature of HD has adverse effects, and that daily HD may be a therapeutic option that is more favorable and should be advanced with more vigor [14, 15], although it is unclear if the results obtained with daily HD with selected patients groups can be obtained in the general HD population.

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