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Implications of the Long Inter-Dialytic Gap: A Problem of Excess Accumulation vs. Excess Removal?

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Abstract

Evidence suggests that patients receiving intermittent maintenance hemodialysis treatments experience higher mortality the day after the long two-day inter-dialytic gap. A new study confirms higher mortality and reports increased hospitalization immediately after the long inter-dialytic interval amongst incident hemodialysis patients in the United Kingdom. Larger fluid accumulation followed by excessive ultrafiltration and abrupt fluctuations in serum potassium concentrations may be among potential factors contributing to the morbidity and mortality of this precarious period.

Keywords

Hemodialysis; inter-dialytic interval; hospitalization; mortality

In many parts of the developed world, maintenance hemodialysis treatment has typically been prescribed as a thrice-weekly regimen with two one-day and one two-day inter-dialytic gaps in-between sessions.(1) Although practice patterns vary across countries, the thrice-weekly hemodialysis schedule has served as an effective means of delivering adequate treatment to large numbers of patients using finite resources.(2) However, there has long been concern that hemodialysis patients may be vulnerable to excess volume and metabolic fluctuations surrounding the long asymmetrical inter-dialytic gaps, given their underlying cardiovascular risk and impaired capacity for fluid, electrolyte, and uremic toxin excretion.(1, 3-5)

Multiple deleterious factors both *during* and *after* the long inter-dialytic gap may lead to heightened morbidity and mortality. Increased sodium and fluid consumption—in part due to social excursions over the weekend—as well as larger accumulation over the two-day

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interval leads to higher inter-dialytic weight gain and pre-dialysis blood pressure, left ventricular hypertrophy and cardiovascular morbidity and mortality, presumably due to 1) supply-demand mismatch, decreased coronary perfusion, and subendocardial ischemia; and 2) an arrhythmogenic cardiac substrate predisposed to sudden cardiac death events.(6) Over the long inter-dialytic interval, total body water may increase in a linear fashion, while blood volume has an initial slow rise followed by a rapid increase during later time intervals.(7) Hence, the initial preferential redistribution of total body water towards the extravascular space may attenuate the abrupt expansion of the intravascular compartment and potential adverse cardiovascular sequelae during the long inter-dialytic gap.(7) Conversely, a more rapid rate of ultrafiltration the day after the long inter-dialytic gap due to the need for excess fluid removal over a fixed session length may lead to intra-dialytic hypotension, myocardial stunning and fibrosis, pre-syncope/syncopal events, and falls.(6) Similarly both extreme hyperkalemia following the long inter-dialytic gap as well as large serum potassium fluxes due to a high intra-dialytic potassium gradient may lead to ventricular arrhythmias (Figure 1). Apart from these fluid and metabolic derangements, more frequent hospitalizations on Monday and Tuesday following the long inter-dialytic gap may result from a "weekend lag effect," i.e., socially conditioned avoidance of hospitalizations during the weekend. Alternatively, heightened mortality the day after the long inter-dialytic gap could be an "after-effect" of differential care over the weekend, relating to reduced staffing, limited availability of tests and procedures, and delays in diagnosis and management

Higher morbidity and mortality amongst hemodialysis patients following the long inter-dialytic gap has previously been shown. In a study of the US dialysis population from 1977-1997, Bleyer *et al.* found that sudden and cardiac deaths were most common on Mondays and Tuesdays, whereas an even distribution of events was observed across all weekdays amongst peritoneal dialysis patients.(3) Amongst hemodialysis patients, there was a higher rate of deaths on Mondays during the Monday-Wednesday-Friday [MWF] schedule vs. Tuesdays during the Tuesday-Thursday-Saturday [TTS] schedule, suggesting that receipt of dialysis after the first weekend night (i.e., Friday) on a TTS schedule may attenuate fluid and solute accumulation over the long inter-dialytic gap. In a similar study of the US hemodialysis population from 2002-2007, higher rates of mortality and cardiovascular hospitalizations were observed on the day after the long inter-dialytic gap(4) except for those with a vintage of <1 year. While accurate residual kidney function (RKF) data were not available, it is possible that higher death risk after the long inter-dialytic gap is abrogated in those with substantial RKF. Although time of death relative to the hemodialysis treatment session could not be ascertained, there was a tendency for higher events on hemodialysis vs. non-hemodialysis days. In another study of 80 US hemodialysis patients, there was a bimodal death distribution such that death events were more common at the end of and immediately after the long inter-dialytic gap, suggesting that accumulation and fluctuations of fluid/uremic toxins with dialysis lead to higher mortality.(8) European and Japanese cohorts have shown a similar pattern of findings in comparison to the US, with some nuanced differences.(5) While heightened mortality risk following the long inter-dialytic interval was pervasive across all three regions, Japanese patients on a MWF schedule had the highest risk of non-cardiovascular mortality and European patients on a TTS schedule had the highest risk of cardiovascular mortality on the day of the last hemodialysis session

of the week (Friday and Saturday, respectively). Whereas these differences may be related to the availability of Sunday hemodialysis schedules in some countries, it was inferred that more aggressive dialysis and ultrafiltration on Fridays/Saturdays in anticipation of long inter-dialytic gap and subsequent intradialytic hypotension and hypokalemia may predispose to higher death risk.

The peril of the post-two-day inter-dialytic period is a critically important topic calling for further dissection. In this issue of *Kidney International*, Fotheringham *et al.* has risen to this challenge by investigating 1) the long inter-dialytic gap's link with hospitalization and death risk, and 2) factors associated with hospitalization and mortality in this context, amongst a well-characterized cohort of 5,864 incident hemodialysis patients who initiated dialysis from 2002-2006 across 36 centers in England.(1) Using data from the UK Renal Registry linked to the Hospital Episode Statistics dataset which captures diagnostic, procedural, and mortality information for all hospitalizations, the investigators uniquely identified three different hemodialysis treatment schedules: MWF, TTS, and Tuesday-Thursday-Sunday (TTSun, in which Sunday is the first day following the long inter-dialytic gap), accounting for 50.2%,47.3%, and 2.5% of treatment-years, respectively. After a median follow-up of 1.3 years, they observed higher hospitalization rates the day after the long inter-dialytic gap across all hemodialysis treatment schedules. In addition, the day following the long inter-dialytic gap was associated with higher mortality rates, largely driven by out-of-hospital deaths.

This study adds new insights to the underlying mechanisms and at-risk subpopulations of the long inter-dialytic gap. First, higher hospitalization rates observed on Monday, Tuesday, and Sunday for patients on MWF, TTS, and TTSun hemodialysis treatment schedules, respectively, do not support the “weekend lag effect” as an explanatory factor for higher admission rates on the day after the long inter-dialytic gap. This is further corroborated by similar rates of hospitalizations observed on the third hemodialysis treatment session of the week, i.e., Friday and Saturday for patients on MWF and TTS hemodialysis treatment schedules. Second, as a high proportion (79%) of out-of-hospital death events were reported on dialysis days in the absence of a corresponding hemodialysis procedural code, the investigators inferred that the majority of these deaths occurred *before* dialysis, supporting fluid/uremic toxin *accumulation* as the likely mechanistic link between the long inter-dialytic gap and mortality risk. However, risk ratios for hospitalization the day after the long inter-dialytic gap vs. the rest of the week were highest for admissions associated with 1) fluid overload and 2) falls/fracture/trauma, suggesting that both fluid accumulation and excess fluid removal ensuing from dialysis are contributory. Third, secondary and sensitivity analyses pointed to subpopulations particularly at-risk during the long inter-dialytic gap. Higher hospitalization rates after the long inter-dialytic gap occurred amongst patients with cardio-pulmonary disease (e.g., heart failure, chronic obstructive pulmonary disease, high pre-dialysis systolic blood pressure), who may be intolerant of fluid perturbations. In contrast to the US study,(4) associations between the long inter-dialytic gap and outcomes were not modified by vintage. Subgroup analyses showed that higher mortality rates after the long inter-dialytic interval were found in whites but not non-whites, in whom no differences in hospitalizations were observed; further studies are needed to understand the

potential role of race/ethnicity contributing to these differential associations. Other strengths of the study include its examination of an incident hemodialysis cohort unaffected by survivor bias; uniqueness of the Sunday hemodialysis schedule in some centers, comprehensive availability of dialysis modality, diagnostic/procedural code, hospitalization, and mortality data using the UK national datasets; and the long follow-up period of up to 7 years.

The study should be qualified by its inability to directly examine several key modifiers, confounders, and/or intermediates of the long inter-dialytic gap—hospitalization/mortality association, including RKF, session length, compliance with dialysis attendance, and serum/dialysate potassium concentrations. Second, defining comorbidity status and indication for hospitalization using administrative data are subject to misclassification. Third, these observations might not be generalizable to hemodialysis patients outside of England where practice patterns and case-mix characteristics differ. Fourth, due to anonymity of the dataset, investigators were unable to conduct validation exercises of the primary data. Lastly, these observational findings are unable to confirm a causal association of the long inter-dialytic interval with hospitalization and mortality risk.

Based on these collective data, we believe that both excess fluid and uremic toxin accumulation and rapid removal with dialysis contribute to the heightened morbidity and mortality of the long inter-dialytic gap. Given the exceedingly high mortality of the hemodialysis population, there is critical need to identify approaches that ameliorate the morbidity and mortality of this precarious period, such as 1) incremental fluid/solute removal (i.e., aiming for a higher dry weight, lower fluid removal goal, and lower dialysis dose the day after the long inter- dialytic gap vs. mid-week targets), 2) eliminating the long inter-dialytic gap with more frequent sessions in those with negligible RKF, 3) longer session lengths immediately following the long inter-dialytic gap, 4) pharmacotherapeutic interventions that reduce excess uremic toxin/solute accumulation and fluctuations (e.g., potassium binders), and 5) which subpopulations would maximally benefit from these interventions. Given the disparate findings with regards to dialysis vintage in some of these studies,(1, 4) direct examination of the impact of RKF and strategies that preserve RKF as a mitigator of the post-two-day inter-dialytic period outcomes are warranted.

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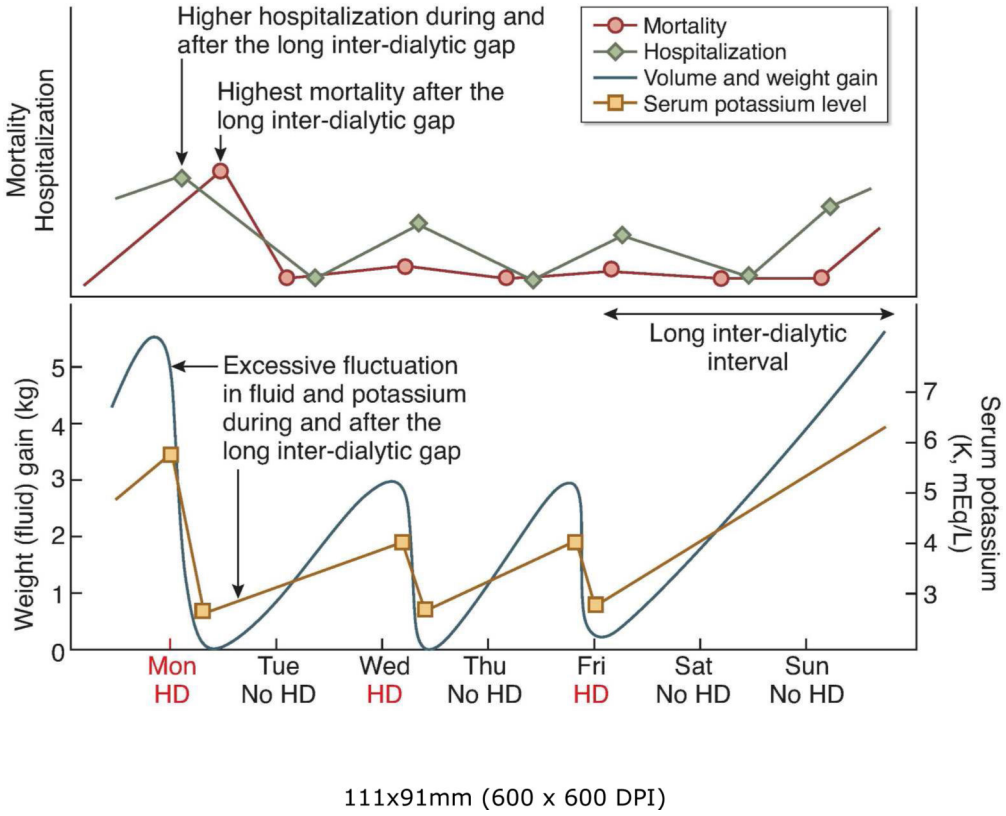

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Figure 1.

Schematic representation of the fluid and electrolyte (potassium, K) fluctuations during a theoretical thrice-weekly hemodialysis schedule of a patient who receives hemodialysis treatment on Monday, Wednesday and Friday.