Port J Nephrol Hypert 2012; 26(3): 221-228
Advance Access publication 10 September 2012

Surrogates in chronic disease: misleading substitutes
Jose Vinhas
Department of Nephrology, Centro Hospitalar de Setúbal. Setúbal, Portugal

Port J Nephrol Hypert 2012; 26(2):133-137
Advance Access publication 08 February 2012

LETTER

Even if surrogates are misleading substitutes, measurement of quality of care is worthwhile

Dr Helena Sá

Consultant, Nephrology
President of National Commission for Monitoring of Dialysis
(Comissão Nacional de Acompanhamento de Diálise – CNAD)

Received for publication: 18/07/2012
Accepted in revised form: 09/08/2012

Sir,

We are concerned about the radical view of the proposal by Dr. José Vinhas[1] that denies the utility of adopting therapeutic thresholds as a tool to promote and evaluate optimal therapy adequacy in dialysis (as is currently adopted in Portugal)[2].

We believe that the problem lies in knowing what we are, in fact, discussing. On one hand, we should consider the existence of clinical end points or outcomes such as mortality, which is, without a doubt, the most important clinical end point in the haemodialysis population. On the other hand, there are surrogate end points or markers, for which Dr. José Vinhas properly points out that "the key criterion for the validity of a surrogate end point is the possibility of predicting the effect of the treatment on the clinical outcome by the effect of the treatment on the surrogate"[1]. Finally, we should also contemplate the therapeutic thresholds (indicators of quality of care, quality of care measures or performance targets) based on a quality measurement programme, whichever it is, that could be chosen (if chosen at all), in order to affect reimbursement of treatment. True surrogate markers for every important clinical outcome should be recommended. However, the lack thereof does not imply that quality measurement is not worthwhile. Otherwise, are we prepared to return to the beginning of technological and process improvements?

To better describe the danger of reducing the evaluation of our clinical practice to surrogate markers selection, we should reflect on the (bad) example of the HEMO Study which supported the continued use of a Kt/V

urea of 1.2, since it could not demonstrate an improvement in outcomes by increasing Kt/V urea above this standard, on conventional thrice-weekly haemodialysis[3]. However, both the HEMO Study and the other large randomised trial into dialysis dose measured by urea removal (the National Cooperative Dialysis Study), did not prove that it is safe to sustain below-standard Kt/V urea and, we do not comprehend Dr. José Vinhas's statement to the effect that "with current environment and prescription patterns, it's unlikely the dose of dialysis will have a significant impact on patient morbidity or mortality"[1,4,5]. We look forward to discovering what kind of other therapeutic thresholds related to adequacy of dialysis Dr. José Vinhas currently relies on: longer treatment times, removal of phosphate and larger molecules associated with high flux, or none, perhaps?[6-12]

All quality measurement programmes deserve continuous and critical evaluation. Although critical evaluation should not be neglected, we anticipate that without a quality surveillance programme, inspired by clinical practice guidelines, we risk less order and poorer organisation. Furthermore, improving quality of care, then, proves to be more difficult. A pertinent but different issue is to decide whether achieving targets for clinical measures or thresholds should, or not, affect reimbursement (as in Germany, the United States and here in Portugal, actually)[2,13].

Sharing this point of view, the National Commission for Monitoring of Dialysis (*Comissão Nacional de Acompanhamento de Diálise – CNAD*) has undertaken a critical review of the current quality of care programme assessed by specific parameters in each dialysis unit[2]. The new proposal has focused on the adoption of a clinical endpoint (mortality), a surrogate marker (definitive vascular access) and two therapeutic thresholds (level of haemoglobin higher or lower than 12 and 9 gr/dL, respectively and eKt/V urea or URR higher than 1.2 and 65%, respectively)[14,15].

We believe that this new proposal will contribute to ameliorating the measurement of quality haemodialysis care. We refuse to narrow our irreplaceable clinical experience and daily practice to the results of few, and by no means representative, trials as they are so frequently underpowered even if of randomised controlled design. For instance, the NCDS was not powered to evaluate mortality as an outcome, and the HEMO Study lacked convincing evidence demonstrating that shorter treatment sessions are safe[3-5]. As researchers of the HEMO Study Group indicate, their results do not rule out benefits of more intensive therapies such as daily treatment (or six times per week) or very long dialysis sessions (more than six hours each)[16]. Several large observational studies suggested that doses of dialysis that were higher than standard doses and the use of dialysis membranes with higher-permeability characteristics (or flux) were associated with lower mortality. The highest long-term survival rates among patients undergoing dialysis treatment three times weekly have been reported by groups that have used high doses and long treatment times[8,17-23].

Following this, the Frequent Hemodialysis Network recently completed two prospective randomised trials examining the effect of more frequent, short-hours and nocturnal haemodialysis compared with standard thrice-weekly treatments[11-12]. Whereas the first frequent short-hours trial reported favourable results in the composite outcomes of death or change in left ventricular mass, the negative results of nocturnal haemodialysis trials cast some doubt on whether intensive home dialysis has any advantages over conventional haemodialysis. Once again, should we abandon haemodialysis intensive therapies? Both trials, although prospective and randomised, were underpowered to detect a mortality effect and none assessed patient quality of life. A large enough randomised, controlled trial of intensive haemodialysis is unlikely to appear in the coming years. Meanwhile, we believe there are a number of significant observational studies that cannot be dismissed[24,25].

It is our belief that until we see large randomised controlled trials revealing true surrogate markers in the dialysis field (if feasible at all), we must trust in the best available evidence to help in our clinical and policy decisions.

Conflict of interest. None declared.

References

1. Vinhas J. Surrogates in chronic disease: misleading substitutes. Port J Nephrol Hypert 2012;26:133-37

2. Gestão Integrada da Doença Renal Crónica – Metas e Objectivos para Monitorização de Resultados em Diálise (Nº: 03/DSCS/DGID DATA: 22/02/08)

3. Eknoyan G, Beck GJ, Cheung AK, *et al*. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002;347:2010-19

4. Lowrie EG, Laird NM, Parker TF, Sargent JA. Effect of the hemodialysis prescription on patient morbidity. N Engl J Med 1981;305:1176-1181

5. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int 1985;28:526-34

6. Hakim RM, Breyer J, Ismail N, Schulman G. Effects of dose of dialysis on morbidity and mortality. Am J Kidney Dis 1994;23:661-669

7. Parker TF III., Husni L, Huang W, Lew N, Lowrie EG. Survival of hemodialysis patients in the United States is improved with a greater quantity of dialysis. Am J Kidney Dis 1994;23:670-680

8. Locatelli F, Martin-Malo A, Hannedouche T, *et al*. Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol 2009;20:645-654

9. Innes A, Charra B, Burden RP, Morgan AG, Laurent G. The effect of long, slow haemodialysis on patient survival. Nephrol Dial Transplant 1999;14:919-922

10. Lacson E, Brunelli SM. Hemodialysis Treatment time: a fresh perspective. Clin J Am Soc Nephrol 2011;6:2522-30

11. Chertow GM, Levin NW, Beck GJ, *et al*. FHN Trial Group. In-center hemodialysis six times per week versus three times per week. N Engl J Med 2010;363:2287-300

12. Rocco MV, Lockridge RS Jr, Beck GJ, *et al*. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. Kidney Int 2011;80:1080-91

13. Vanholder R and al. Reimbursement of Dialysis: A Comparison of Seven Countries. J Am Soc Nephrol 2012;23 *(published online ahead of print June 7, 2012)*

14. KDOQI clinical practice guidelines and clinical practice recommendations for vascular access 2006. Am J Kidney Dis 2006;48[Suppl 1]:S176-S322

15. Mendelssohn DC, Ethier J, Elder SJ, *et al*. Haemodialysis vascular access problems in Canada: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS II). Nephrol Dial Transplant 2006;21:721-28

16. Correspondence to Editor. Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis. N Engl J Med 2003;348:1491-1494

17. Covic A, Goldsmith DJ, Venning MC, Ackrill P. Long-hours home haemodialysis – the best renal replacement therapy method? QJM 1999;92:251-60

18. Innes A, Charra B, Burden RP, Morgan AG, Laurent G. The effect of long, slow haemodialysis on patient survival. Nephrol Dial Transplant 1999;14:919-22

19. Wolfe RA, Ashby VB, Daugirdas JT, Agodoa LY, Jones CA, Port FK. Body size, dose of hemodialysis, and motality. Am J Kidney Dis 2000;35:80-88

20. Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA. Dialysis dose and body mass index are strong associated with survival in hemodialysis patients. J Am Soc Nephrol 2002;13:1061-6

21. Marshall MR, Byrne BG, Kerr PG, *et al*. Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients. Kidney Int 2006;69:1229-36

22. Miller JE, Kovesdy CP, Nissenson AR, *et al*. Association of hemodialysis treatment time and dose with mortality and the role of race and sex. Am J Kidney Dis 2010;55:100-112

23. Brunelli SM, Chertow GM, Ankers ED, *et al*. Shorter dialysis times are associated with higher mortality among incident hemodialysis patients. Kidney Int 2010;77:630-6

24. Walsh M, Culleton B, Tonelli M, Manns B. A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life. Review.Kidney Int 2005;67:1500-8

25. Suri RS, Nesrallah GE, Mainra R, Garg AX, *et al*. Daily hemodialysis: a systematic review. Clin J Am Soc Nephrol 2006;1:33-42

REPLY ▶