and a full-thickness cartilage lesion visualized on magnetic resonance imaging (MRI).

Both treatment groups had improvement over the 2-year period. There were no significant differences in the change in the KOOS4 score from baseline to 2 years between the group assigned to rehabilitation plus early ACL reconstruction and the group assigned to rehabilitation plus optional delayed ACL reconstruction. The results indicate that the patient reported outcome scores with KOOS4 as primary outcome variable as well as most of the pre-specified secondary outcomes, which included pain, symptoms, function in activities of daily living, function in sports and recreation, knee-related quality of life, general health status, activity level, and return to pre-injury activity level at 2 years were similar in the 2 groups and early reconstruction of ACL in all patients did not offer any definite advantage over the other group which had supervised physiotherapy followed by optional ACL reconstruction. The incidence of adverse events such as arthrofibrosis, graft ruptures and other complications were also similar in both groups. By adopting the strategy of rehabilitation and optional delayed reconstruction, as many as 61% of the patients did not have to undergo surgical treatment without compromising the overall results.

The study is of particular relevance in the Indian context as a significant proportion of patients with acute ACL injuries can be managed appropriately without surgery. This would decrease the workload on our already over-burdened health sector, both public and private.

There are certain limitations of the study and a few questions are left unanswered. First and foremost is the issue of ACL injuries in professional athletes. As is evident from the study, a significant portion of patients, 23 of 59, from the optional reconstruction group remained unstable and symptomatic even after a supervised physiotherapy protocol for a reasonable period and required surgical intervention (mean 11.6 months), it is difficult to adopt this approach in a professional athlete as the time lost during physiotherapy may cost the athlete heavily. The second limitation of the study is the lack of emphasis on data on objective assessment of the knees on stability, namely pivot shift test and instrumented assessment of abnormal translation. It is evident from the data, although not amply discussed, that the results of objective assessment of the knee stability were significantly inferior in the optional reconstruction group: normal Lachman test 29% *v.* 65%, normal result on pivot shift test 47% *v.* 75% and mean laxity of 8.3 mm *v.* 6.6 mm on KT-1000 arthrometry. It is debatable whether a comparable score on subject-based outcome measures would also mean a comparable risk of developing osteoarthosis later in the presence of inferior results on objective assessment of knee instability in the optional reconstruction group. Long term follow up would be required to answer this question.

REFERENCES

1 Andersson C, Odensten M, Gillquist J. Knee function after surgical or nonsurgical treatment of acute rupture of the anterior cruciate ligament: A randomized study with a long-term follow-up period. *Clin Orthop Relat Res* 1991;**264:**255–63.
2 Arnold JA, Coker TP, Heaton LM, Park JP, Harris WD. Natural history of anterior cruciate tears. *Am J Sports Med* 1979;**7:**305–13.
3 Feagin JA Jr, Curl WW. Isolated tear of the anterior cruciate ligament: 5-year follow-up study. *Am J Sports Med* 1976;**4:**95–100.
4 Casteleyn PP, Handelberg F. Non-operative management of anterior cruciate ligament injuries in the general population. *J Bone Joint Surg Br* 1996;**78:**446–51.
5 Johnson RJ, Beynnon BD, Nichols CE, Renstrom PA. The treatment of injuries of the anterior cruciate ligament. *J Bone Joint Surg Am* 1992;**74:**140–51.
6 Noyes FR, McGinniss GH, Grood ES. The variable functional disability of the anterior cruciate ligament-deficient knee. *Orthop Clin North Am* 1985;**16:**47–67.

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Time to move to more frequent haemodialysis?

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SUMMARY

The Frequent Hemodialysis Network (FHN), funded by the National Institute of Diabetes and Digestive and Kidney Diseases and supported by the Centers for Medicare and Medicaid Service of the USA, designed two randomized controlled trials (RCTs) to compare the effect of more frequent (6-times weekly) haemodialysis (HD) treatments with the conventional thrice-a-week dialysis. One of the studies used daily in-centre HD whereas the other looked at home nocturnal HD.[1]

This paper reports the result of the daytime in-centre HD study, conducted among adult HD patients who were expected to survive at least 6 months. There were two primary end-points: A composite of death and 12-month change in left ventricular (LV) mass as assessed by cardiac MRI, and a composite of death and 12-month change in

self-reported physical health score of the RAND 36-item health survey. A number of secondary outcome parameters (LV mass, physical health component of RAND-36, Beck Depression Inventory score, cognitive function by Trail Making Test, serum albumin, serum phosphorus, dose of erythropoiesis-stimulating agent [ESA] and blood pressure) were also compared. It was determined *a priori* that favourable effects on both co-primary composite outcomes would be required to consider the trial to have had positive results. Risk of intervention was assessed by comparing the need for intervention related to vascular access. Patients with residual renal function were excluded. A total of 378 patients were enrolled and 245 randomly assigned to frequent (125 patients) or conventional (120 patients) treatment for 12 months. A total of 32 patients in the conventional group and 24 patients in the frequent HD group were excluded from analysis because of various reasons. The mean (SD) times per dialysis sessions were 213 (28) and 154 (25) minutes and the total dialysis times per week were 10.4 (1.6) and 12.7 (2.2) hours in the 2 groups, respectively. The weekly standard Kt/Vurea (the product of the urea clearance and the duration of the dialysis session normalized to the volume of distribution of urea) was significantly higher in the frequent HD group (3.54 [0.56] *v.* 2.49 [0.27]). Per session ultrafiltration was lower (2.12 [0.74] *v.* 3.06 [0.99] L) but the weekly ultrafiltration more (10.58 [3.8] *v.* 8.99 [3.03] L) in the frequent HD group. Frequent HD was associated with significant benefits with respect to both co-primary composite outcomes (hazard ratio for death or increase in LV mass, 0.61; 95% confidence interval [CI] 0.46–0.82; hazard ratio for death or a decrease in the physical-health composite score, 0.70; 95% CI 0.53–0.92).

Subgroup analyses revealed no difference by gender, history of heart disease, anthropometric volume, duration of end-stage renal disease, or presence or absence of residual kidney function. In terms of secondary outcome, frequent HD was associated with improved control of hypertension and hyperphosphataemia but made no difference to cognitive performance, self-reported depression, serum albumin concentration, or use of erythropoiesis-stimulating agents. On the downside, frequent HD patients were more likely to undergo interventions related to vascular access than were patients assigned to conventional HD (hazard ratio, 1.71; 95% CI 1.08–2.73). The authors concluded that as shown in observational studies, frequent HD, as compared with conventional HD, was associated with favourable results with respect to the composite outcomes of death or change in LV mass and death or change in a physical-health composite score but prompted more frequent interventions related to vascular access. The authors hypothesized that the benefit could have been as a result of the greater between-group differences in terms of small solute clearance, improved control of other metabolic products, or simply a more physiological (frequent) removal, reflected by a lower inter-dialytic weight gain.

COMMENT

The future of patients with end-stage kidney disease forever changed in 1960 when widespread availability of dialysis treatment became possible following the development of a vascular access device.[2]

While largely considered a miracle of modern medicine, the less charitable sometimes call dialysis an acceptable alternative to death. This is because despite numerous technical advances, the long term outcome of dialysis patients remains unsatisfactory. Only 44% of those between 45 and 64 years will live through 5 years of dialysis treatment, and just 21% of dialysis patients between 65 and 74 years of age will survive through 5 years. Also, health is rarely restored; patients frequently develop cardiovascular complications and require hospitalization.[3]

The success of dialytic treatment depends upon adequate removal of 'uraemic' solutes, measured traditionally by clearance of urea, and the achievement of euvolaemia as assessed by salt and fluid balance and normalization of blood pressure. Traditionally, this has been sought to be achieved through three 4-hour sessions of HD every week. For a long time, researchers chased small solute clearance until the HEMO study showed that improving small solute clearance did not result in improved mortality, rate of hospitalization or health-related quality of life.[4] It was also suggested that the high mortality was a result of delayed initiation of dialysis. This notion was put to bed by several observational studies and a randomized controlled trial (IDEAL).[5] This suggested the need for an alternative approach.

The intermittent nature of current-day HD treatment results in large fluctuations in the 'milieu interieur'. Right from the initial days, it has been thought that more frequent treatment would lead to improved outcomes, a view supported by a wealth of observational data.[6–16] In fact, some studies suggest that the survival rates almost match those after renal transplantation![10] More frequent dialysis (daytime in-center or nocturnal home HD) is associated with better blood pressure control, improvement in mineral and bone parameters, reduced requirement of erythropoiesis stimulating agents and improved quality of life. However, the increased cost prevented its widespread use.

Faced with the negative results of the HEMO study, the National Institutes of Health, USA created a Task force that suggested the need of a RCT of more frequent dialysis; hence, the FHN network and the two studies.

These trials took 10 years to complete. Ideally, such a trial should look at hard end-points such as death, cause-specific death, or hospitalization. However, the sample size was insufficient to determine the effects of the experimental approach on these outcomes. This was because of difficulties in recruitment. The following barriers to recruitment were identified: lack of patient motivation and unwillingness to change the present arrangement, lack of family support, fear of the procedure, cost of home renovations (for nocturnal home HD) and transportation (for in-centre HD), advanced age and child care issues.[17] There were additional issues that prevented recruitment in the home (nocturnal) HD study.

Despite the difficulty in recruitment, the study appears to have achieved the goals of randomization and controlling bias thus validating the outcomes of significant reduction in morbidity and mortality in the 6 times a week cohort. Hence the issue of internal validity is satisfied.

The real test of the findings will be in the external validity, i.e. how generalizable the results are to the entire (global) HD population? Right off the bat, the populations in the trials were younger than the United States Renal Data System (USRDS) dialysis population.[18] The conventional HD patients received dialysis at a dose higher than that recommended currently, and the mortality in both groups was very low, even in the control group the death rate at 1 year was only 7.5%, far lower than the US average of 18.5%, as noted in the accompanying editorial.[19]

Normally, validation is achieved by conducting large observational studies to confirm the findings of the RCT. In this case, a number of such studies already provide external validation to the FHN study.

Data from other parts of the world, such as Western Europe, Australia and New Zealand show improved outcomes with longer, slower and gentler dialysis done at home or in-centre. Taken together, the findings reinforce the concept of the impact of improved middle molecule clearance and better volume control by increased frequency and duration of dialysis on outcome.

While the positive results of this study have generated some excitement, it is interesting to note that the other FHN study, i.e. the long nocturnal HD, failed to show a benefit as compared to the conventional HD. The data were presented at the recent annual meeting of the American Society of Nephrology. We must await publication of the full results for detailed analysis, but intuitively one would think that of the two forms of more frequent HD, this would have been more likely to show benefit because of the more physiological nature of the modelled effect.[20] One likely problem is of insufficient numbers, as the initial goal of recruiting 250 patients was dropped to 90 because of recruiting difficulties!

Having looked at the benefits, we must examine the issue of harms. The obvious one is the need for more frequent vascular access-related interventions. Progress must be achieved in this area. The accompanying editorial[19] suggests that the complications could have been avoided by using the buttonhole method of needle insertion, in which cannulation is done repeatedly at the exact same site, allowing the development of a track in a path lined by scar tissue.

A recent opinion piece (published before the result of this study were announced)[3] examined the progress (or lack of it) made in the last half-century of providing population-based HD and suggests how successes can be achieved. Of the several suggested action points, two stand out: avoidance of indwelling catheters for vascular access and meticulous attention to control of extracellular volume and mitigation of LV hypertrophy and fibrosis through longer, more frequent dialysis. Previous studies have shown that treatments targeted to reducing LV mass even of a lesser magnitude than that achieved in this study affect death and cardiovascular events favourably.[21] Attention to LV mass should probably replace the focus on atherosclerotic coronary artery disease. Reduction in LV mass requires meticulous extracellular fluid control and achievement of normotension. More frequent dialysis of longer duration with less per-session ultrafiltrate have been suggested as important for achieving this goal. It is postulated that progress in these two areas, along with continued attention to other elements, such as meticulousness of care in the first 120 days, avoidance of infection and reduction in dietary salt intake would unlock the stagnation in outcomes of dialysis therapy of end-stage kidney failure and allow it to realize its full potential of prolonging life and alleviating disability.

It would be interesting to see how the nephrology community worldwide, and in the USA in particular, uses these data and whether this will change patient and/or nephrologist behaviour. Considering that recruitment in the trial was difficult, it remains to be seen whether the findings would prompt patients in the USA to accept more frequent HD. Calls are already being issued to reduce suffering and death in America's dialysis units by implementing what some believe to have known for decades: more frequent and longer duration dialysis saves lives.

Finally, what does it mean for the Indian dialysis population? In contrast to the West, where the focus is on improving outcomes, we struggle to make dialysis available to our patients. Most patients die without getting any.[22] Even among those who are on HD, twice a week HD is considered the standard of care except in a tiny minority treated in private dialysis units. Unless major changes are made in the way dialysis is funded in India, analysing such studies will not progress beyond an academic exercise.

REFERENCES

1 Suri RS, Garg AX, Chertow GM, Levin NW, Rocco MV, Greene T, *et al.* Frequent Hemodialysis Network (FHN) randomized trials: Study design. *Kidney Int* 2007;**71:**349–59.
2 Scribner BH, Buri R, Caner JE, Hegstrom R, Burnell JM. The treatment of chronic uremia by means of intermittent hemodialysis: A preliminary report. *Trans Am Soc Artif Intern Organs* 1960;**6:**114–22.
3 Parker T 3rd, Hakim R, Nissenson AR, Steinman T, Glassock RJ. Dialysis at a crossroads: 50 years later. *Clin J Am Soc Nephrol* 2010 Dec 9.
4 Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, *et al.* Hemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002;**347:**2010–19.
5 Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, *et al.* IDEAL Study. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;**363:**609–19.
6 Walsh M, Manns BJ, Klarenbach S, Tonelli M, Hemmelgarn B, Culleton B. The effects of nocturnal compared with conventional hemodialysis on mineral metabolism: A randomized-controlled trial. *Hemodial Int* 2010;**14:**174–81.
7 Shaldon S. First use of nocturnal hemodialysis. *Kidney Int* 2009;**76:**230.
8 Schorr M, Manns BJ, Culleton B, Walsh M, Klarenbach S, Tonelli M, *et al.* The effect of nocturnal and conventional hemodialysis on markers of nutritional status: Results from a randomized trial. *J Ren Nutr* 2010 Jul 20. [Epub ahead of print]
9 Pierratos A. Does frequent nocturnal hemodialysis result in better outcomes than conventional thrice-weekly hemodialysis? *Nat Clin Pract Nephrol* 2008;**4:**132–3.
10 Pauly RP, Gill JS, Rose CL, Asad RA, Chery A, Pierratos A, *et al.* Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. *Nephrol Dial Transplant* 2009;**24:**2915–19.
11 Lacson E Jr, Wang W, Lester K, Ofsthun N, Lazarus JM, Hakim RM. Outcomes associated with in-center nocturnal hemodialysis from a large multicenter program. *Clin J Am Soc Nephrol* 2010;**5:**220–6.
12 Hodge MH. The path to a paradigm shift in hemodialysis. *Hemodial Int* 2010;**14:** 5–10.
13 Chan CT, Lovren F, Pan Y, Verma S. Nocturnal haemodialysis is associated with improved vascular smooth muscle cell biology. *Nephrol Dial Transplant* 2009;**24:**3867–71.
14 Bayliss G, Danziger J. Nocturnal versus conventional haemodialysis: Some current issues. *Nephrol Dial Transplant* 2009;**24:**3612–17.
15 Agar JW, Hawley CM, George CR, Mathew TH, McDonald SP, Kerr PG. Home haemodialysis in Australia: Is the wheel turning full circle? *Med J Aust* 2010;**192:** 403–6.
16 Agar JW. Nocturnal haemodialysis in Australia and New Zealand. *Nephrology* (*Carlton*). 2005;**10:**222–30.
17 Pipkin M, Eggers PW, Larive B, Rocco MV, Stokes JB, Suri RS, *et al.* Recruitment and training for home hemodialysis: Experience and lessons from the Nocturnal Dialysis Trial. *J Am Soc Nephrol* 2010;**5:**1614–20.
18 Rocco MV, Larive B, Eggers PW, Beck GJ, Chertow GM, Levin NW, *et al.* FHN Trial Group. Baseline characteristics of participants in the Frequent Hemodialysis Network (FHN) daily and nocturnal trials. *Am J Kidney Dis* 2011;**57:**90–100.
19 Twardowski ZJ, Misra M. 'Daily' dialysis—Lessons from a randomized, controlled trial. *N Engl J Med* 2010;**363:**2363–4.
20 Greene T, Daugirdas JT, Depner TA, Gotch F, Kuhlman M; Frequent Hemodialysis Network Study Group. Solute clearances and fluid removal in the frequent hemodialysis network trials. *Am J Kidney Dis* 2009;**53:**835–44.
21 Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol* 2009;**4 Suppl 1:**S79–S91.
22 Jha V. End-stage renal care in developing countries: The India experience. *Ren Fail* 2004;**26:**201–8.

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