Haemodialysis renal replacement therapy—do we need more research?

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Introduction

The answer to the question is in the affirmative for two reasons. The first can be expressed by the cliché ‘knowledge is power’, since the dialysis world certainly needs more power to deal with the unacceptable morbidity and mortality of the population on all forms of dialysis. The second is the fascination with the myriad of individual pathophysiological problems which tantalize with partially proven hypotheses and potential therapeutic successes. In regard to the second reason, there was a time when dialysis was seen only as an imperfect mode of saving lives, but certainly not worthy of research at the highest academic level. Clearly this is no longer the case. A personal list of items requiring research is briefly discussed, with the strong caveat that enumeration by others would be quite different.

International variations in mortality and morbidity

Reaching the level of national rivalry, these differences undoubtedly exist even in equally well-dialysed patients. Consideration of background mortality may well explain these, at least in part. Inspection of the MONICA [1] and other data [2] show that the rate of coronary events in the general population is approximately half as high in countries such as France, Spain, and Japan as it is in the US. Even in the US, the standardized mortality ratio correlates with background population mortality [2]. The improved survival of African-Americans in the US, and of Asians both in Japan and in the US, supports the concept that genetics, environment, diet, etc. influence dialysis mortality. The possible role of physician practice is currently being explored by a huge study being conducted in the US, Germany, UK, France, Italy, Spain, and Japan, and dealing with randomly selected representative fraction of the entire dialysis populations of those countries [3].
Cardiovascular disease

The much higher incidence in the US, particularly in the younger population, is striking and has invited intense interest as models for the general population. So many separate pathogenetic schemes are currently presented that it is impossible to realistically understand the relative importance of each. Of particular interest are the relationships between inflammation, oxidative stress, activation of metalloproteases, lipids, coagulation, and atherosclerosis [4–6]. The aetiology of the inflammation is not understood, nor is the value of non specific anti-inflammatory approaches. The importance of abnormalities in Ca–P metabolism on vascular and myocardial function need clarification, particularly in relation to sudden death due to arrhythmia. Techniques capable of providing information in longitudinal studies are needed.

Uraemic toxins

While there is general acceptance that a certain level of a thrice-weekly dialysis prescription for small molecules (best expressed as Kt/V urea) is required as a minimum (in that mortality is higher at lower doses), the apparent value of more frequent dialysis schedules (so far not definitely proven) suggests that single solute kinetics of molecules other than urea has a crucial role. For example in the usual thrice-weekly dialysis schedule, phosphorus removal is ineffectual because of its rapid decline in serum concentration a short time after the beginning of the treatment. With daily dialysis, double the number of treatments now increase efficiency and permit effective phosphorus removal. We are ignorant to a much larger extent concerning the kinetics of purported uraemic toxins such as of small proteins [7]. Application of new sorbents that remove such molecules could change current perspectives on uraemic toxicity.

Intradialytic treatment quantitation

New technologies deal with the measurement of dialysis efficacy by on-line devices. A typical example is the direct measurement of conductivity clearance as a surrogate for urea clearance [8,9]. Other on-line ‘sensors’ permit intra-dialytic electrolyte balance determination [10], measurement of blood volume changes as a guide to ultrafiltration [11,12], and blood temperature modulation [13]. Feedback devices integrating many of the above technologies are beginning to display some benefits [14], but application on a large scale is still not usual. Clearly, factors affecting hypotension are more numerous than the above and the variable roles of the sympathetic nervous system and refilling from the lymphatic system need clarification and further integration.

Haematocrit

The availability of erythropoietin has revolutionized the treatment of anaemia. However, the implications of raising haematocrit to normal values (and beyond during ultrafiltration) with consequent increase in viscosity in patients with vascular diseases are not known or understood.

Vascular access

While the superiority of AV fistulae for vascular access is largely unquestioned, new technical developments continue to emerge. Subcutaneous vascular access [15] may be useful in specific dialysis schedules (daily, home treatments), particularly with the use of new ‘locking solutions’ reducing infection rates. Prediction of vascular access failure is a growth industry with development of many methods and techniques to simplify and reduce costs of an early diagnosis [16]. The effective value of access flow measurement require further elucidation.

‘Dry weight’

Simple in concept compared to the world of uraemic toxins, the ultrafiltration component of the prescription is often a matter of inspiration. When patients can spend a large fraction of their lives being dialysed it is easier to remove larger quantities of fluid, but the challenge is with shorter dialysis times. New approaches to estimation of dry weight [17] are required since it seems clear that normotension is more frequent when dry weight is reached.

Nutrition

Conceptually, the role of primary malnutrition, i.e. protein–caloric deficit as the major cause of hypoalbuminaemia (a major indicator of mortality) has been replaced by the notion that inflammation influences both albumin synthesis and appetite. Unanswered questions are the relative roles of these two factors in the dialysis population and the effect of supplemental feeding in hypoalbuminaemia patients with high levels of C-reactive protein and other acute-phase reactants.

Economic analysis and survival

Availability of adequate reimbursement is gradually increasing in some countries in parallel with economic development while, at least in relative terms, it is decreasing in countries long accustomed to dialysing most potential candidates. Research is required into means of increasing cost efficiency technically and operationally so that adverse financial changes can be
dealt with realistically. Opportunities to reduce supply costs are less likely to occur than the development of biofeedback systems, resulting in safe control of the dialytic procedure and less need for skilled personnel. This, however, may conflict with the real world where older and sicker patients increase in number in haemodialysis programmes. We cannot expect technology to become a substitute for clinical judgement and bedside patient care. But that does not mean that we see an end to technological development. Many other areas of renal replacement require further investigation, particularly physical rehabilitation, haemodialyser design, fluid handling, and pre-ESRD management.

After this short and certainly incomplete response, some final issues should be considered:

In the past 40 years at regular intervals there was always someone who has said that everything has been discovered in haemodialysis and that further research was a waste of time. This statement has recurrently been challenged by enthusiastic investigators and new findings continue to be made.

Today we cannot be content because we keep our patients alive. We should give them a chance to live a normal life and to achieve, if not a complete, then certainly a more satisfactory, rehabilitation than at present.

Whenever a physician walks into the dialysis unit, patients ask if anything new is on the horizon for them.

Haemodialysis treatment for acute patients is still in a primitive stage compared with chronic HD. There is much to be understood and explored. Not attempting to understand all the above issues on HD is like cutting the cables of a suspension bridge crossing the valley between the present and the future. The need for further research in dialysis is obvious but we must postulate that research is done at the highest level. The investigator who tries to tackle the above issues must go far beyond nephrology and include basic science as well as other clinical disciplines.

References