

A controlled trial of treatment for steroid resistant nephrotic syndrome

JF Soothill, PN McLaine, DG Cottom, OH Wolf [1967]

Children with steroid resistant nephrotic syndrome were allocated randomly into two series, one receiving cyclophosphamide (3mg./Kg. expected weight for height/day) and the other hydroxychloroquine (5mg./Kg. expected weight for height/day). Results were assessed by creatinine clearance, blood urea and immunochemical estimation of the excretion of albumin. Response to cyclophosphamide was often dramatic and there was a significant difference in the log mean week (-1) - log mean week (8) for 24-hour albumin excretion, albumin excretion, albumin clearance, clearance of albumin expressed as a percentage of creatinine clearance, and urine albumin/creatinine concentration between the two groups.

These four parameters were compared as methods of measuring the effect of therapy in nephrotic syndrome, and the latter, the simplest for practical purposes, was found to be as satisfactory as the others, providing continuous quantitative data from gross proteinuria to normal values.

This abstract reports the first randomised controlled trial [RCT] ever presented to the Renal Association, although to my knowledge it was not subsequently published in a journal.

In the 1960s RCTs were just beginning to emerge in nephrology, and the early efforts were in glomerular disease. The first ever nephrology RCT was probably the MRC trial of corticosteroids in nephrotic syndrome which began in 1961 but was not published until 1970¹ [then as now it is a fundamental rule usually lost on funding agencies and optimists that trials always take longer from start to finish than anyone predicted]. The first published RCT in nephrology of which I am aware was presented to the Renal Association a year later in 1968 and published in 1969².

When this abstract was presented John Soothill [1925-2004] was Renal Association Secretary, and had recently moved to Great Ormond Street Hospital. Though more an immunologist than a nephrologist he played a key role in these early trials in nephrotic syndrome. In the days before the establishment of BAPN in 1973, paediatricians played a full and active part in all aspects of the Renal Association

¹ Black DA, Rose G, Brewer DB. Controlled trial of prednisone in adult patients with the nephrotic syndrome. *Br Med J.* 1970; 3 :421-6

² Sharpstone P, Ogg CS, Cameron JS. Nephrotic syndrome due to primary renal disease in adults: II. A controlled trial of prednisolone and azathioprine. *Br Med J.* 1969 ;2:535-9.

Inevitably perhaps this abstract is light on the kind of detail now *de rigueur* for triallists. How were entry criteria defined? How many patients were studied? How were they randomised? It was I am sure not blinded. At that size, it can be called no more than a pilot study. But.... they did it!

Presumably those recruited mostly had primary FSGS although we are not told the biopsy findings [if indeed any of the children were biopsied]. And of course we have no idea how many had mutations in podocyte proteins which might have influenced whether or not they were likely to respond to immunosuppressive therapy.

Notice also the choice of outcome measure in this study of nephrotics. Urine albumin/creatinine ‘..... **the simplest for practical purposes, was found to be as satisfactory as the others, providing continuous quantitative data from gross proteinuria to normal values.**’

Nothing new there then. Paediatricians for practical reasons took this much more rapidly into practice than adult nephrologists, who for a couple of generations have continued to struggle in clinical practice and research with 24 hour urine collections, and still debate whether a ‘spot’ urine is sufficiently accurate³. Though I admit that personally I have not ordered a timed urine collection to measure proteinuria for more than a decade.

Most of the nephrology trials emerging in those early days were in glomerular disease, and particularly in steroid-sensitive nephrotic syndrome in children – and from the results of those trials, those of us caring for adults even now continue to extrapolate. But a trial in 1967 in steroid-resistant nephrotic syndrome is remarkable given that forty years later we still live with uncertainty about how best to manage this condition. To my knowledge the whole world of nephrology has, since 1967, produce only a dozen RCTs of reasonable quality in childhood steroid-resistant nephrotic syndrome, and a paltry five in adult FSGS.

Why did we fail in the UK, let alone worldwide to build on this promising start in the late 1960s and develop a properly organised pipeline of trials? It is a popular pastime debating the reasons, and we quite correctly compare ourselves unfavourably with almost any other branch of internal medicine. We should not make too many excuses; there is no escaping that it is a dismal failure which means we continue in much ignorance about management of glomerular disease, not to mention other aspects of nephrology.

³ Fine DM et al. A prospective study of protein excretion using short-interval urine collections in patients with lupus nephritis. *Kidney Int* 2009; 76: 1284-1288