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Editorial Comment

EDITORIAL COMMENT

The rise and rise of randomized clinical evidence in Sub-Saharan Africa

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Abstract

Sub-Saharan Africa is facing a rising tide of chronic disease, including chronic kidney disease, but the current research literature provides little evidence to guide the practice of nephrology in resource-poor settings. In this issue of CKJ, Waziri & Bello present a trial of two formulations of intravenous iron for patients with anaemia of chronic kidney disease in Nigeria. This study typifies a growing body of work from researchers from low-middle income countries addressing the evidence gaps that they meet in their everyday practice. Collaboration with clinical trialists and health economists from the global renal research community is suggested as an important way to expand, at low cost, the randomized evidence-base in this region.

In this issue of *Clinical Kidney Journal*, Waziri and Bello [1] present a randomized trial of intravenous low molecular weight iron dextran (LMWID) versus iron sucrose for anaemia of chronic kidney disease (CKD). The trial was conducted in Lagos, Nigeria with the purpose of comparing the efficacy and safety of the two most commonly available intravenous iron preparations in sub-Saharan Africa. Their study of 67 patients with a mean eGFR of 23 mL/min/1.73 m^2 and mean haemoglobin of 92 g/L demonstrated no significant difference in the proportion of patients achieving a 10 g/L rise in haemoglobin—32.4% with iron sucrose (1000 mg in five divided doses) versus 21.9% with LMWID (1000 mg in four divided doses)—and a similar mean increase in haemoglobin in both groups—6 ± 9 versus 4 ± 7 g/L. There were too few adverse events recorded to be sure if there was a difference in safety profile between arms.

Intravenous iron has been shown to be superior to oral iron for the treatment of anaemia in CKD patients [2]. A variety of intravenous iron formulations are available. They are generally considered to be of equivalent efficacy but offer differing administration profiles, adverse event rates and costs [3]. LMWID, although less expensive, is associated with an increased rate of allergic adverse reactions [4]. A randomized trial of 370 patients comparing LMWID, ferric gluconate or iron sucrose observed a significantly increased number of serious adverse events with LMWID (6.2/100 patients) versus ferric gluconate (1.8/100 patients) and iron sucrose (0.9/100 patients) [5]. In the present study, one of the 33 patients suffered an apparent anaphylactic reaction to a test-dose of LMWID—in keeping with prospective studies suggesting a rate of adverse reactions with LMWID of 2–8%, including a 0.6% rate of anaphylaxis [6, 7]. Whether the cost of managing this risk outweighs the savings is unknown.

In Sub-Saharan Africa, as in other low and middle income regions, a dramatic epidemiological transition from communicable to non-communicable disease is under way. This change is being driven in part by a high prevalence of hypertension and diabetes [8, 9] and presages a rising tide of CKD in countries ill equipped to respond to it. A representative example is Kinshasa (Democratic Republic of the Congo), where 1 in 10 adults has diabetes and >1 in 4 have hypertension [10]. A meta-analysis of 22 studies in Nigeria, including 5005 adults with a mean age of 45 years, of whom 25% had hypertension and 25% were HIV positive, found the prevalence of significant CKD (eGFR < 60 mL/min/1.73 m^2) was as high as 10% [11]. Meagre health budgets in this region can mean that access to basic kidney care is limited. Nigeria's gross domestic product (GDP) has increased rapidly over the last decade and now stands at US$568 billion or US$3115 per

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capita for its 180 million people—meeting the World Bank definition of a lower middle income (LMIC) country [12]. But its government spends only 0.9% of its GDP on health, well below the low and middle income country average of 3.0% and a fraction of the global mean of 6.8% [13]. Bello *et al.* [13] previously reported that the majority of end-stage renal disease patients in Nigeria are dialysed less than once weekly and that the mean haemoglobin at the time of commencing haemodialysis is 73 g/L [14]. In addition to managing hypertension, diabetes and albuminuria with established treatments, Nigerian nephrologists need to make rationing decisions on CKD therapies that are routinely available in other LMIC countries. Waziri and Bello [1] report a price of US$85.10/1000 mg dose of iron sucrose and US$55.20/1000 mg of LMWID. This contrasts with the average per capita annual health care spending of US$94 in 2012 (most of which was out-of-pocket expenditures by the patient) [15].

Trial results from high-income countries may be useful to inform decision makers in Nigeria about intravenous iron, but ideally, research should be developed and conducted where it is most needed, reflecting local conditions and constraints. Yet the absence of an African nephrology evidence base is very apparent. Analysis of data from the International Clinical Trials Registry, which collates international trial registries including the Pan African Clinical Trials Registry, identified that, of the 2887 trials concerning patients with renal disease registered between 2000 and 2014, only 29 (1%) included patients from Africa [16]. Of these, 22 were from South Africa and the remainder from Egypt and Tunisia. No registered nephrology trial included patients from non–South African sub-Saharan Africa—a region representing 12% of the world population. This paucity of trials may in part reflect the paucity of institutional frameworks supporting high-quality research practice. Although Nigeria and South Africa now mandate ethics committee review for all human research [17], in most of sub-Saharan Africa it has been stated that the institutions required to foster autochthonous health research exist 'more in theory than in reality'[18]. Therefore, the present trial represents an important commitment to the generation of high-quality clinical evidence by nephrologists in Sub-Saharan Africa. The investigators should be commended for making the important decision to randomize their patients and observe them prospectively.

In retrospect, a trial of this scale was unlikely to demonstrate clinically important differences in efficacy between the different forms of parenteral iron therapy—if they do exist. As renal anaemia is characterized by haemoglobin variability [19], the possibility cannot be entirely excluded that an increase in haemoglobin similar to that observed in a minority of subjects in both treatment arms might also have been observed even with a placebo. Similar increases are often observed in the placebo arm of blinded randomized epoetin studies. The important differences in the two treatment arms were always more likely to be in adverse events and in cost [20].

Future research should be informed by discussion among African nephrologists as to the priority renal research questions in Africa. Collaboration is also likely to be key to delivering appropriately designed and powered trials to address any new research agenda. Clinical trialists in the global renal community stand ready to work with groups in Africa to design new trials that could include prospective collection of local health economic data. Good local cost-effectiveness data are critical to making informed choices about the costs of treating renal anaemia, bearing in mind that this will include the costs of monitoring for potential adverse events and treating them as they arise. In this context, a factorial randomized study of good quality generic recombinant epoetin (perhaps sourced from China or India) with parenteral iron therapy—separately and together—might be a valuable next step in the continued exploration of this key aspect of renal care in resource-constrained settings. It may well be demonstrated that a judicious combination of both is most cost effective in Africa, just as it is in the West.

This study, and the others that will follow it, provide a basis for optimism. The institutional infrastructure underlying national health research systems continues to improve in Africa [21] and interest in pragmatic comparative efficacy research to facilitate the efficient use of finite health care resources is growing [22]. Streamlined study designs, culturally appropriate consent paradigms [23, 24] and the use of routinely collected electronic health care data [25, 26] may allow large studies to be completed at a fraction of the cost of industry-funded international trials. As African nephrology trials grow in number and quality, a growing cadre of experienced nephrologists/researchers will be established, who should take full advantage of the expertise and help offered by the world's leading renal research centres. The first-ever meeting of the International Congress of Nephrology in Africa in 2014 was a landmark event that strengthened collaborative ties and showed the way forward. With this in mind, *Clinical Kidney Journal* looks forward to publishing more local randomized trials from Africa examining similar practical research questions. We are confident they will have a valuable impact worldwide on the care of CKD patients in resource-constrained settings.

Conflict of interest statement

None declared.

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