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Pro/Con Debate

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A well-conducted randomized trial that establishes no benefit of therapy is an important medical advance

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Background

As physicians, we continually strive to understand disease processes and predict how they will affect our patients. However, our greatest skill lies in our ability to intervene and change the natural history of a disease, i.e. change a poor outcome which otherwise would have occurred. Many types of interventions are used in the care of renal patients, from pills, to procedures and dialysis, to alternative ways to deliver health care. All would agree that interventions need to be evaluated to determine if they are beneficial, without harm, and cost-effective in a system of finite resources.

A randomized, controlled clinical trial (RCT) is an experimental method used to evaluate the effectiveness of an intervention. RCTs are conducted when an intervention shows the potential for health care improvement, but there is collective uncertainty as to the true benefits of the intervention [1]. This uncertainty is in fact essential to the clinical trial paradigm, as otherwise clinical equipoise would be violated, and in most cases it would not be ethical to randomly assign patients between the intervention to be tested and a control intervention. This is true both when the control treatment is a placebo and when the control entails administration of an active treatment reflecting standard therapy [2]. A logical consequence of the uncertainty required to maintain equipoise is that a substantial proportion, in fact the majority, of well-conducted RCTs must be negative.

When an intervention is found to be efficacious in a well-conducted RCT (referred to here as a positive trial), the therapy is often rapidly adopted into standard medical care [3–5]. While positive trials still need subsequent real-world evaluations for unanticipated deleterious effects [6, 7], in general a positive trial is viewed as an important medical advance for the betterment of patient health. Examples of recent positive trials in nephrology include mycophenolate for active lupus nephritis [8], angiotensin-converting enzyme inhibitors in advanced chronic kidney disease [9], combination ACE inhibitor and angiotensin-receptor blocker therapy in non-diabetic renal disease [10], education for patients with chronic kidney disease to choose self-care dialysis [11], polysporin triple antibiotic ointment for haemodialysis central venous catheter insertion sites [12] and hydration with sodium bicarbonate plus *N*-acetylcysteine in patients undergoing emergency percutaneous coronary intervention [13].

A RCT can also establish the absence of a clinically important benefit of an intervention on a primary outcome, a result that in this context is referred to as a 'negative' trial. Examples of recent negative trials in nephrology include atorvastatin for diabetic patients receiving haemodialysis [14], intravenous dopamine in critically ill patients [15], high dialysis dose and membrane flux in maintenance haemodialysis [16], angioplasty for renal artery stenosis [17], and plasma exchange when myeloma presents as acute renal failure [18]. Aside from the issue of equipoise, the occurrence of such negative findings is essential to the conduct of evidence-based medicine; the absence of negative trials would indicate a failure of the RCT paradigm to refute the clinical hypotheses evaluated in RCTs when these hypotheses are in fact false. This capacity of experimental evidence to refute untrue hypotheses is fundamental to the advancement of science [19]. Given the reality of finite resources for medical treatment, the identification of non-efficacious therapies is also essential to allow the available resources to be distributed to those therapies that are demonstrated to be efficacious. Further, it is our position that negative RCTs, when they occur, often represent important medical advances in their own right for the care of our patients. We highlight examples where negative clinical trials have influenced theory and practice.

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Assumptions for the argument

We take our position under the following assumptions, which apply irrespective of whether the trial turns out to be negative or positive:

(1) It is ethical and practical to study the intervention in a RCT. For example, technologies in some areas of medicine are advancing so quickly that the intervention studied in a RCT is no longer relevant by the time the RCT is reported.

(2) The RCT is well conducted using methods to minimize bias (e.g. concealment of allocation, adequate generation of the allocation sequence, double blinding and a minimal number of patients lost to follow-up [20–22]). The trial also has adequate statistical power to rule out a minimal clinically important benefit of the intervention, if in truth this benefit exists [23].

(3) The outcome studied in the trial is clinically important, avoiding a separate debate on the potential for misleading results with surrogate measures [24].

(4) The intervention is applied appropriately in the RCT, and patients are followed for a necessary period to allow a 'biological' effect of the intervention to be exerted [25].

(5) RCTs represent a rigorous method to convince physicians, the public and government regulatory agencies as to the benefits (or lack thereof) of an intervention. For this reason they are accepted as one of the highest levels of evidence to evaluate treatment effects [26,27]. Despite the intensive resources needed to conduct RCTs, there is an agreement that some need to be conducted.

(6) The debate excludes RCTs designed to prove non-inferiority, which have a different framework for the definitions of 'positive' and 'negative' in the current discussion.

Negative RCTs do influence theory and future research

Well-conducted negative RCTs can result in a paradigm shift and a revolution in scientific thinking. To illustrate the point, take the scenario that major observational studies suggested that the high mortality in ESRD patients on haemodialysis might be improved by increasing the delivered dose of dialysis [28]. This theory was tested in a large RCT [16]. Patients on conventional, three times weekly haemodialysis were randomized to receive usual dose (equilibrated Kt/V of 1.05 per session) versus high dose (equilibrated Kt/V of 1.45 per session). These increased doses were delivered primarily by increasing dialysis session time. The RCT was negative; there were no significant differences in either the primary analysis or in four pre-specified secondary analyses between the two groups with respect to overall mortality, hospitalizations or serum albumin-based end-points. This RCT prompted a re-evaluation of existing theories for the kinetics of small and middle molecule solute removal on haemodialysis [29]. Urea and other small toxic solutes follow first-order kinetics, with the rate of solute removal proportional to the concentration of solute [30]. Consequently, most solute removal occurs at the start of haemodialysis, with decreasing removal rates as the haemodialysis session proceeds [31]. During the last hour of a 4.5-h haemodialysis session, very little solute is removed in comparison to the first 3 h. Thus, increasing dose by increasing dialysis session time on conventional haemodialysis results in very minimal increments in total urea and small toxic solute removal. Similarly, the relatively short increases in time on conventional haemodialysis do not result in substantial increases in removal of toxic middle molecules [32], such as β2-microglobulin, implicated in dialysis amyloidosis [33], nor in phosphate, implicated in cardiovascular risk and death [34]. Finally, increasing haemodialysis session time within the setting of conventional, three times per week dialysis does not ameliorate the problem of chronic extracellular fluid accumulation, a major contributing factor in the development of hypertension and cardiovascular risk [35].

The negative results of the HEMO trial redirected attention from modifications to therapy within the constraints of conventional, three times per week dialysis to alternative treatment schedules that may be better suited to address these physiological considerations. For example, dialysis performed daily for 2 h, six times per week, would be predicted to be an improvement over conventional haemodialysis being performed for 4 h, three times per week, despite total weekly dialysis time remaining constant. Given that one is dialyzing against the steepest portion of the urea concentration curve each day, daily haemodialysis would be predicted to have higher efficiency than conventional haemodialysis, resulting in greater weekly small solute, middle molecule and phosphate removal [32,36]. Preliminary studies have highlighted the potential merits of daily haemodialysis [37], and the intervention is now being tested in a larger RCT [38].

In addition to redirecting the focus of research from hypotheses that are falsified by their primary analyses, secondary analyses of data collected in negative trials have also often had a major scientific impact. For example, while the primary analyses of the Modification of Diet in Renal Disease Study failed to demonstrate a benefit of protein restriction for CKD patients, secondary results from this study led to the development of widely used methods for quantification of renal function [39] and have contributed to the characterization of the course of progression of kidney disease and it consequences [40]. Secondary analyses from the dialysis study noted above have similarly led to advances in the quantification of dialysis dose [41] and the understanding of potential biases in observational studies [42]. Results from this study in subgroups such as female gender [43] have contributed to the ongoing debate on the question of whether optimum dialysis dose is characterized by utilization of a constant Kt/V in all patients.

Negative RCTs do influence practice

Many interventions are used in patient care even prior to being studied in a RCT. There is ample evidence that the results of completed RCTs influence the subsequent use of the therapy, with negative studies followed by negative shifts in use. Take for example the use of prolonged plasma exchange for multiple sclerosis, a technical procedure not unlike dialysis, with a comparable risk profile [44,45]. A small prospective study indicated a superior outcome

in patients who received immunosuppression and plasma exchange compared to those who received immunosuppression alone [46]. Use of plasma exchange for multiple sclerosis increased the year after this report was published. Subsequently a larger RCT was conducted, which included a placebo group and used end-points based on blinded observation [47]. The trial showed no benefit for plasma exchange, which resulted in a decrease in activity that persisted over the subsequent decade. Although to our knowledge no empirical evaluation has been reported, based on our clinical experience similar negative shifts in use also occurred after important negative RCTs in renal medicine: angioplasty for renal artery stenosis [17], protein restriction in chronic kidney disease [48], plasma exchange for myeloma kidney [18], normalization of haemoglobin in patients receiving haemodialysis [49] and deliberate attempts to target a higher dialysis dose (equilibrated Kt/V of 1.45 per session) amongst haemodialysis patients [16]. The negative RCTs also influence recommendations in subsequent clinical practice guidelines. Negative shift in therapy use may be even more dramatic, if the trial demonstrates evidence of harm in addition to lack of benefit [50].

Conclusion

The need for careful scientific evaluation of new interventions is undeniable. As with any type of research, RCTs have their advantages and disadvantages, and can be subject to abuse. However, when a RCT is conducted with due diligence, the result, whether positive or negative, provides an important opportunity to advance knowledge and improve patient care.

Conflicts of interest statement. None declared.

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