Transplant International

INVITED COMMENTARY

Time to reflect, time to move on

Emily R. Thompson[1,2] & Colin H. Wilson[1,2]

1 Institute of Transplantation, The Freeman Hospital, Newcastle-upon-Tyne, UK
2 NIHR Blood and Transplant Research Unit, Cambridge/Newcastle, UK

Correspondence
Colin H. Wilson, Institute of Transplantation, The Freeman Hospital, Newcastle-upon-Tyne NE7 7DN, UK.
Tel.: 01912 448 310;
e-mail: colinwilson2206@gmail.com

Transplant International 2020; 33: 1185–1186

Received: 28 May 2020; Accepted: 1 June 2020

Stenting the ureter during renal transplantation was a source of controversy for decades, and Ooms *et al.* [1] have grappled with this topic again in this issue of Transplant International. The team in Rotterdam have designed and implemented a research trial, after the first iteration of the Cochrane review on ureteric stents [2], published back in 2005.

The novelty of this particular trial lies in the intervention, an external suprapubic stent which has the added attractive benefit of permitting clinicians to identify the specific source of urine and proteinuria (transplant or native). In certain transplant situations, though not all, this may well be of considerable value. The predialysis patient receiving a deceased donor kidney at high risk of delayed graft function for instance. Of course, an extra external foreign body also brings potential risks and the stent was associated with more haematuria and longer hospital stays—but significantly reduced major urological complications when compared with no stent at all. However, this conclusion does not represent a major step change in knowledge—all these assertions have already been made in the updated Cochrane meta-analysis published in 2013 which concluded that—"studies comparing selective stenting and universal prophylactic stenting, whilst difficult to design and analyse, would address the unresolved quality of life and economic issues".

Archie Cochrane came to popular attention in 1971 with his paper on "Effectiveness and Efficiency", a scathing critique on the lack of evidence in modern medicine at the time [3]. These thoughts were crystallized in the formation of the Cochrane Collaboration. A major international organization funded by healthcare providers determined to establish value for money and limit the harms of ineffective interventions. This initiated the assimilation of vast quantities of randomized controlled trial evidence, the birth of the meta-analysis and the now ubiquitous "Forest plot", a tool now as familiar as the pie chart introduced by the healthcare researcher Florence Nightingale back in the 1850s.

The Cochrane logo depicts the results of seven randomized controlled trials examining the evidence for effectiveness of maternal steroids to prevent neonatal respiratory distress in premature babies [4]. Each trial was underpowered, and it was only the Cochrane review, bringing together all the evidence that finally established the use of steroids as best practice. On the back of this, no further trials have been performed [5]. One of Archie Cochrane's specific concerns had been around the wasteful repetition of underpowered and poorly designed trials when the real evidence was already available.

Organ transplantation, unlike many areas of surgery, has always been heavily invested and orientated around

doi:10.1111/tri.13670

scientific methods. Immunosuppression trials have been at the forefront of medical advances, and landmark trials are readily quotable. In the more technical areas though there has been a tendency for individual surgeons and teams to be more insular in their thinking, appropriately powered large multicentre randomized trials are the exception rather than the rule.

The Cochrane review on ureteric stents in renal transplantation, when it was first published in 2005 [6], acknowledged there remained some controversy around ureteric stents, and the Ooms trial was designed in response to this knowledge gap. However, further statistical analysis in a second iteration of the review concluded that routine ureteric stenting could now be confidently recommended [6]. This second review identified specific areas for further study—particularly around the duration and design of stents. Reassuringly, trials have subsequently emerged to address these further questions and a separate Cochrane review in 2018 concluded that internal stents did appear to be superior at preventing urinary tract infections when compared with external stents, and these could be removed within 2 weeks of transplant [7]. The role of external stents could therefore best be described as controversial at present.

Currently, there are three trials listed online with clinical trials.gov investigating the use of ureteric stents, and even a cursory glance is enough to confirm there is unnecessary overlap and repetition in this tiny number. Multiple fragmented and underpowered trials that do not encompass the full scope of the research question can result in a poorer evidence base. Clinical trials take significant time and energy and are expensive. In the past when the incidence of transplant complications was high, relatively small trials with only hundreds of patients could answer the questions. Now, the incidence of complications is lower, trial design needs to be rethought, and most questions cannot be answered with anything less than thousands of patients.

Looking forward, there is no doubt that patients would benefit from collaboration, centralization and co-ordination of trials to ensure that the right trial is performed at the right time. Various organizations are in a position to take this leadership role, but at present there is no clear and obvious acknowledged route to standardization. The Standardised Outcomes in Nephrology-Kidney Transplantation Group (SONG-Tx) have come closest by establishing themes and core outcome sets, and within countries like Canada and the United Kingdom, there are well-respected networks being formed to frame research priorities with patients at the heart of the discussions. However, the scale of the issues will demand international co-operation to ensure the best use of resources.

In many ways, we as transplant surgeons are victims of own success. The early outcomes for kidney transplant surgery are now so good that significant major complications are of the order of maybe only 1 or 2%. This means that for the next step change, thousands or perhaps even tens of thousands of patients will need to be randomized to see meaningful results. Archie Cochrane, when asked how far clinicians should go with randomization, said "we should randomise until it hurts" [3]. As a community, we need to embrace this, look forward, establish the correct questions in international collaborations and then be prepared to randomize every patient to move the science forward.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

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