Debate: CON Position

Formal Assessment of Donor Kidney Function Should Be Mandatory

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Introduction

Recipients of living kidney transplantation have a graft half-life almost twice that of recipients of deceased kidney transplants. The introduction of safe surgical and anesthetic techniques and the perpetual shortage of deceased kidney donors has led in part to an increase in living donors. Furthermore, there is an acceptance of altruistic kidney donors and more centers are participating in ‘donor swaps’ leading to more donors coming forward for assessment as potential living kidney donors. These numbers are likely to increase even more with the introduction of techniques to transplant across the ABO barrier and in cases of positive cross-match.

The classical technique of assessing the renal function is a 24-hour creatinine clearance (CrCl); however, there is a significant variability of test results due to inaccurate 24-hour urine collection, patient compliance with instructions on the collection technique and normal variation from day to day [1]. Issa et al. [2] evaluated the performance of CrCl, Modification of Diet in Renal Disease, the re-expressed MDRD equations with standardized creatinine, and the Cockcroft-Gault formula as compared with ¹²⁵I-iothalamate GFR in 423 living kidney donors; variable performance was seen among different GFR estimations, with CrCl being the poorest.

To prevent some suitable donors being turned down due to borderline CrCl, there is a push to standardize the technique of measuring renal function in potential living kidney donors. One technique is a nuclear scan using iothalamate as an exogenous marker. We present three lines of argument why nuclear scan GFR may not be used routinely for this purpose.

Ioiothalamate GFR: Technique and Variability

For urinary clearance of ¹²⁵I-iothalamate, a radioactive exogenous filtration marker is used in the measurement of glomerular filtration rate (GFR). Since an adequate (5 ml/min) urine flow is important and necessary to calculate clearance, hydration with a water load of 20 ml/kg is a prerequisite. A bolus subcutaneous injection of iothalamate is then given. To block the uptake of the radioactive tracer by the thyroid gland, ‘cold’ iodine is administered at the time of the ¹²⁵I-iothalamate administration. This requirement precludes its use in subjects with allergy to iodine, shellfish or iodinated contrast material. After equilibration for an hour, four consecutive urine collections are obtained by voluntary voiding. Water intake to replace the volume voided is necessary, which in some patients could lead to nausea or in rare

instances hyponatremia. Furthermore, since complete voiding is essential for calculating clearance, conditions that interfere with voiding (e.g. the stress of 'on-demand voiding' or in case of an older donor, subclinical bladder pathology) would affect test results. Five serum samples bracketing the urine samples are obtained from an indwelling intravenous catheter in the arm contralateral to the iothalamate-administered arm [3]. The GFR is calculated as the renal clearance of iothalamate for each individual period and the overall GFR is calculated as if the clearance periods were one long period, and it is adjusted for body surface area. The rapid clearance of iothalamate in patients with potentially normal GFR has major implications for the timing of the blood samples. These need to be accurately timed as there would be a marked difference in the concentration of the marker with small changes in time (and therefore the value of the calculated clearance). The procedure requires about 6 h and needs specialized personnel. In the event of the patient coming to the test mildly dehydrated, euvolemia needs to be restored and a satisfactory urine flow established prior to starting the test (contributing further to time). This technique overall overestimates the GFR when compared to the gold standard of inulin clearance. In a clinical trial setting, the median coefficient of variation for repeated measurement of urinary iothalamate clearance was 6.3% over 3 months [4]. It is possible that in routine clinical practice, this figure would be much higher.

Radiation Risk

While debated, a recent study suggests that radiation exposure from medical imaging may be responsible for 1–3% of cancers worldwide [5]. A potential donor is exposed to a small, albeit finite dose of radiation during the course of donor work-up. The use of a radioactive tracer like iothalamate would add to this risk. It is also likely that the donor may need postoperative imaging studies and additional radiological studies unrelated to the kidney donation – all adding to the total radiation exposure in the lifetime. Furthermore, women are at slightly higher risk of developing cancer when compared to men exposed to the same dose of radiation. This is worrisome, as women outnumber men in being living kidney donors [6]. However, increasingly there is a trend towards the use of 'cold' (i.e. non-radioactive) iothalamate.

Based on the new safety data, the FDA is considering new safeguards for CT scanners and other imaging ma-

Table 1. Cost (in USD) associated with measuring GFR using ^{125}I -iothalamate and $^{99\text{m}}\text{Tc}$ -DTPA

	Cost per dose	Technical fee	Professional fee	Total estimate ¹
^{125}I -iothalamate	21	325	55	396
$^{99\text{m}}\text{Tc}$ -DTPA	20	325	55	395
^{14}C -Inulin	<10	325	55	<385

¹ Fees are based on Medicare rates and do not include shipping, shelving, disposal or differences in institutional charges.

chines to prevent patients from receiving unnecessary radiation exposure which research has shown could cause 29,000 new cases of cancer a year (http://www.usatoday.com/news/washington/2010-02-09-fda-radiation-scans_N.htm?obref=obinsite).

Cost of Nuclear Scans

Although radionuclide measurement of GFR is the best overall index of renal function, determining this measurement is costly, invasive, time-consuming and highly dependent on collection accuracy. Radionuclide assessment of GFR is not widely available and in some cases the performance of these tests is not practical as is the case with kidney donors who should have no biochemical evidence of kidney disease or risk factors for kidney disease prior to donation. The cost associated with measuring GFR using ^{125}I -iothalamate, $^{99\text{m}}\text{Tc}$ -diethylenetriamine pentaacetate ($^{99\text{m}}\text{Tc}$ -DTPA), two of the commonly employed methods in comparison to inulin, are shown in table 1 [7–10]. In addition to the cost of raw materials, facility and professional fees, expenditures for safety and disposal are incurred. Furthermore, unless these compounds are used frequently, each determination will be expensive due to rapid decay. This is in contrast to 24-hour CrCl and equations used to estimate GFR, which have no added cost, although interpretation of estimated GFR should take into consideration accuracy of specimen collection, obesity, children, the elderly as well as the presence or absence of biochemical and structural changes in the kidney.

Conclusion

To summarize, iothalamate scans suffer from operator variability and the technique is not standardized for measuring renal function in potential donors. The discordance between measured and estimated GFR by as much as 30% has been attributed to the imprecision of the iothalamate GFR measurement in a recent study [11]. The technique is time-consuming, lasting more than 6 h, with at least two venipunctures needed for conducting the test. Secondly, it is associated with substantial expenditure that may not always be reimbursed. Thirdly, there is the potential of radiation injury to a donor and finally, most centers are very conservative in the selection process of potential donors using the existing methods of assessing renal function [12]. Indeed, in a

recent meta-analysis of general population cohorts, all-cause mortality was constant between estimated GFR values of 75 and 105 ml/min. This strengthens the argument that a precise estimate of GFR between these values may not be critical [13]. We therefore do not advocate the routine use of iothalamate for this purpose, but do however encourage focused research in reliable, reproducible and safe techniques of measuring renal function, such as cystatin C and β -trace protein in potential kidney donors [14].

Disclosure Statement

The authors do not have any financial interest in the products discussed in this editorial.

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