Continuous infusion of low-dose Iohexol measures changing glomerular filtration rate in critically ill patients

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TITLE

Continuous infusion of low dose Iohexol (CILDl) measures changing glomerular filtration rate in critically ill patients

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CONFLICTS OF INTEREST

None declared

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ABSTRACT

Objective: Measurement of changing glomerular filtration rate (GFR) in acute kidney injury (AKI) remains problematic. We have previously used a continuous infusion of low dose iohexol (CILDl) to measure GFR in stable subjects and postulate that changes $>10.3\%$ in critically ill patients indicate AKI. Our objective is to explore the extent to which CILDl can be a measure of changing GFR during AKI.

Design: clinical observational exploratory study

Setting: adult intensive care unit.

Patients: Three patient groups were recruited: *Nephrectomy group* - predictable onset of AKI and outcome ($n=10$); *Surgery group* - predictable onset of AKI, unpredictable outcome ($n=11$); *AKI group* - unpredictable onset of AKI and outcome ($n=13$).

Interventions: CILDl was administered for 24-80h. Plasma (Cl_P) and renal (Cl_R) iohexol clearances were measured at timed intervals.

Measurements and main results: Kidney Disease: Improved Global Outcomes (KDIGO) AKI criteria were fulfilled in 22 patients (*Nephrectomy*=5, *Surgery*=4, *AKI*=13); CILDl demonstrated AKI in 29 patients (*Nephrectomy*=10, *Surgery*=8, *AKI*=11). Dynamic changes in GFR were tracked in all patients. In Nephrectomy group, Cl_R decreased by an expected 50% ($50.8 \pm 11.0\%$). Agreement between Cl_P and Cl_R improved with increasing duration of infusion: bias of Cl_P versus Cl_R at 48h was $-0.1 \pm 3.6 \text{ mL/min/1.73m}^2$ (Limits of agreement: -7.2 to $7.1 \text{ mL/min/1.73m}^2$). Co-efficient of variation of laboratory sample analysis was 2.4%.

Conclusions: CILDl is accurate and precise when measuring GFR and tracks changes in patients with differing risks of AKI. CILDl may provide a useful standard against which to test novel biomarkers for the diagnosis of AKI.

MAIN TEXT

INTRODUCTION

An improved method of measuring changing glomerular filtration rate (GFR) during acute kidney injury (AKI) would be of immense benefit. We need a method of properly evaluating biomarkers, which to date have been compared with flawed serum creatinine (SCr) measurements, and found to be wanting. Accurate assessment of AKI is required to facilitate dosing of renally-excreted drugs (1), to identify progression to renal replacement therapy (RRT) (2) and to predict those patients most vulnerable to the development of chronic kidney disease (CKD). In research, an improved measurement of GFR would help elucidate the temporal relationship between changing GFR during AKI and pathophysiological consequences.

AKI is defined by increased SCr concentration or reduced urine output (3). Both parameters have limitations in critically ill patients (4).

Theoretically, exogenous filtration markers have advantages over endogenous markers when measuring GFR during AKI. Measurements are not influenced by diet, metabolic processes or body habitus, and are independent of the time of the insult causing AKI. Single bolus injection (SBI) of Iohexol has been used to measure GFR in critically ill patients (5,6), but SBI has methodological limitations. Stable GFR is needed for accurate interpretation – the elimination constant changes during AKI. Multiple administrations are required to measure changing GFR, leading to larger administered volumes than with continuous infusions, increasing potential for toxicity. Prolonged washout periods are needed for complete elimination before the next dose is administered. Changes in volume of distribution (V_d) or non-renal clearance ($Cl_{NON-RENAL}$) in critically ill patients mean that a prolonged time is required before plasma clearance (Cl_P) is equivalent to renal clearance

(Cl_R). Continuous infusions of Inulin (7) and EDTA (8) have been used to measure GFR in critically ill patients but only for less than 4 hours. This is too short for understanding the impact of changes in GFR and development of AKI.

We have previously developed a continuous infusion of low dose Iohexol (CILDl) as a measure of GFR in stable subjects over a range of GFR (28-128mL/min/1.73m²) (9). Accuracy of CILDl was confirmed with the SBI method. Mean intra-individual variation in Cl_P was $<10.3 \pm 7.4\%$, and variation in Cl_R was $<6.9 \pm 4.7\%$ (9).

We hypothesise that variations in excess of these limits suggest AKI is present and that CILDl can accurately and precisely measure changing GFR during AKI. The aim of this study is to explore CILDl as a measure of changing GFR in patients with different risks of developing AKI.

METHODS

Detailed methods are outlined in supplementary online material

Study registration and ethical approval

The UK Clinical Research Network (<http://public.ukcrn.org.uk/>) adopted the study (Reference: 13391). Ethical approval was obtained from Queen's Square research ethics committee (reference: 12/LO/1179). The Declaration of Helsinki (2008) (10) was adhered to throughout.

Patients

The study took place in an adult general intensive care unit. Three patient groups were selected: 1) *Nephrectomy*: Patients due an elective nephrectomy and thus a predictable reduction in GFR of approximately 50% (*defined onset of injury; predictable*

outcome). 2) *Surgery*: Patients due elective major vascular surgery. These patients have a high risk of post-operative AKI (11) (*defined onset of injury; unpredictable outcome*). 3) *AKI*: Emergency patients admitted to ICU meeting Kidney Disease: Improved Global Outcomes (KDIGO) AKI criteria (3) (*unpredictable onset of injury; unpredictable outcome*).

Inclusions

- Patients over 18 years due an elective nephrectomy or major vascular surgery admitted to ICU post-operatively, or
- Patients meeting KDIGO-AKI criteria (urine output or SCr) in ICU (3).

Exclusions

See supplementary online material.

Iohexol administration and sampling

Iohexol was administered via a central venous catheter. A loading dose was administered over 2 minutes (9) and followed by a continuous infusion of Iohexol (Omnipaque 300®; 12) at 0.5mL/h (343.5mg/h) for up to 80h (13). Plasma samples (0.5mL) were taken for Cl_p at 30 mins, 1h, 2h and 4h on day 0, and at 08:00h, 10:00h, 18:00h and 20:00h on days 1-3 from an arterial catheter. Urine samples were taken for Cl_R between plasma samples on day 0 and between subsequent morning plasma samples and evening plasma samples. Time zero was considered to be the time of commencing the infusion. Infusions were commenced within 1h of surgery in *Surgery* and *Nephrectomy* groups.

Laboratory procedures and GFR calculation

Plasma and urine Iohexol concentration were measured by high performance liquid chromatography / electrospray tandem mass spectrometry (LC-MSMS) (Online supplementary material). Baseline eGFR was obtained from admission eGFR (14) for elective patients or from hospital notes, if within the last 6 months. The following formulae were used:

$Cl_P \text{ (mL/min)} = [\text{Iohexol infusion rate } (\mu\text{mol/min})] / [\text{plasma Iohexol concentration } (\mu\text{mol/mL})]$, adjusting for body surface area (BSA) (15).

$Cl_R \text{ (mL/min)} = [U \times V] / P$, where U =urine Iohexol concentration ($\mu\text{mol/L}$), V = volume of urine (mL) per unit time (min), and P = mid-time point plasma Iohexol concentration ($\mu\text{mol/L}$), adjusting for (BSA) (15).

Agreement with KDIGO and outcomes

Iohexol GFR measurements and KDIGO-AKI criteria were observed and classified according to whether subjects met KDIGO and CILDI criteria for AKI: KDIGO-positive (K_{pos}), KDIGO-negative (K_{neg}), CILDI-positive (C_{pos}), CILDI-negative (C_{neg}). Length of stay (LOS) in ICU and hospital, development of CKD within 1 year, need for renal replacement therapy (RRT), and death were recorded. CILDI defined AKI as GFR loss greater than 10.3% (9).

Statistical methods

The data have been graphically explored and summarized according to their nature. Cross sectional (one measurement per individual) have been summarized through means, medians, standard deviations and inter quartile ranges whilst categorical data have been summarized as proportions. Parametric or non-parametric tests have been tailored to

variables' nature. For hierarchical longitudinal data (multiple measurements per individual through time) nonlinear mixed models have been employed. Details are given in the supplementary material.

The analysis is not aiming at inferring differences between clinical groups. They differ by their default clinical definition. Rather, the statistical techniques used are exploratory, with the view of opening up novel methods or indicators which can contribute to the AKI definition.

RESULTS

Screening, enrolment, demographics.

Eleven subjects were enrolled into *Nephrectomy* and *Surgery groups*, and 13 into the *AKI group* (Table 1). One patient in the *Nephrectomy group* was excluded from analysis due to difficult venous access.

GFR.

Cl_P and Cl_R were calculated for each measurement taken on days 1-3. Measurements at 24h are shown in Table 2.

Agreement between Cl_P and Cl_R

Agreement (16) between Cl_R and Cl_P improved with increasing duration of the infusion (Figure 1).

Clinical and Laboratory Accuracy

Measured loss in GFR (Cl_R) at 24h in the Nephrectomy group was $50.8 \pm 17.6\%$ as hypothesized from the loss of one kidney (Table 2, Supplementary Figure 3). For the laboratory analysis of samples, coefficient of variation (CV) for measuring Iohexol was 2.4%, ($n=180$ samples).

AKI misdiagnosis and outcomes

Iohexol Cl_R and Cl_P are compared with 1h- and 4hCrCl at 14h (Table 3). KDIGO-AKI criteria would have missed AKI in 9 patients (*Nephrectomy group: 5, Surgery group: 4*); three subjects meeting KDIGO-AKI criteria did not have AKI when measured by CILDI (Table 4). Patients who were *Kneg/Cpos* had higher proportion of CKD at 1 year than *Kpos/Cneg*.

DISCUSSION

Summary of results

We have used CILDI to measure GFR during AKI over the range encountered in critically ill patients, despite potential fluctuations in V_d and third space accumulation of fluids that may occur.

Demographics are shown in Table 1. *The Surgery group* had a reduced baseline eGFR reflecting the increased co-morbidities in this group. APACHE-II score was highest in the *AKI group* and lowest in *Nephrectomy group*. This was an expected observation related to the varying clinical presentations and complexity of disease.

There was no difference between Cl_P and Cl_R in all groups when GFR was measured at 24h (Table 2). Agreement between Cl_R and Cl_P improved at later stages of the infusion, suggesting a longer period is required for equilibration either caused by a change in $Cl_{NON-RENAL}$ in critical illness or due to increased Vd .

Bland-Altman analysis (16) showed agreement between Cl_P and Cl_R improves with longer duration of infusion, with <1% bias and acceptable limits of agreement in later stages (Figure 1).

All nephrectomy patients underwent surgery for unilateral renal cell carcinomas and 10 had baseline eGFR >50mL/min/1.73m². One patient had an eGFR 39.7mL/min/1.73m² and we measured differential renal function. GFR was equal in both kidneys. The remaining patients had uncomplicated disease and we therefore expected a 50% reduction in GFR following nephrectomy. The observed 50.8% reduction at 24h (Fig 1 and Supplementary Figure 3) suggests that CILDI may provide an accurate measure of GFR.

Brenner's theory suggests an immediate increase in single nephron GFR (SNGFR) following nephrectomy (17). Increases in blood flow and SNGFR have been observed in animal studies (18). Data are inconsistent in human studies: some confirm increased single kidney GFR several days post nephrectomy (19), others suggest it is delayed for up to 36 months (20). Increased blood flow to the remaining kidney has been reported post-nephrectomy (19) but there is a paucity of studies investigating GFR in the immediate post-operative period. We observed increasing GFR after 24h following nephrectomy, although numbers were too small for complete statistical analysis.

The 10.3% difference in Cl_P and 6.7% difference in Cl_R to define AKI is a significant contrast to KDIGO-AKI criteria where a rise in SCr >50% is required (3), resulting in a different proportion of patients meeting criteria for AKI. This is not unusual when different methods

of defining AKI are compared (21). Using CILDI criteria, KDIGO-AKI criteria miss AKI in 5 patients in the *Nephrectomy group*, 4 in the *Surgery group*, and erroneously attribute AKI to 2 patients in the *AKI group*. All patients who were Kpos/Cneg (Table 4) had oliguria and raised SCr at 24h. Creatinine kinetics studies estimate a GFR reduction of 50% must occur to increase SCr by 100% (22), (i.e. stage 2 KDIGO-AKI (3)). To further evaluate our method, we looked at the rate of AKI if defined by a 10.3 % reduction in GFR and also if defined by a 50% reduction in GFR measured by CILDI to define AKI. In both situations, CILDI would detect more AKI than stage 1 KDIGO criteria (Table 4). We chose not to enrol a “control” group of ICU patients without KDIGO-criteria AKI because we would miss false negatives of KDIGO. Using KDIGO-negative AKI patients to define the limits of precision for CILDI-AKI would inevitably show no difference to KDIGO, and would thus render our method susceptible to the flaws of using creatinine-based definitions as comparators.

SCr is a poor marker of GFR in critically ill patients and may not increase as predicted by creatinine kinetic modelling (22). Its formation may be reduced and its secretion increased in critical illness (23) and sepsis (24) and fluid resuscitation may dilute SCr. This combination of factors and the ensuing dynamic changes may result in AKI being under-diagnosed or even over-diagnosed. Other endogenous markers have not yet proven to be sensitive and specific enough in a heterogeneous group of patients or when onset of the insult causing AKI is unknown. However, they have only been tested against SCr.

Studies have suggested 4hCrCl is a useful surrogate for changing GFR during AKI (25) and we have used it previously to evaluate the use of calculated GFR in AKI (26). Our data suggest it lacks sufficient precision to be useful clinically (Table 3). 1hCrCl may be a better choice than 4hCrCl when assessed against Cl_R of Iohexol.

Our data are too few to investigate outcomes fully, but 8 of 9 patients who were *Kneg/Cpos* developed CKD, whereas none of the 3 patients who were *Kpos/Cneg* developed CKD within 1 year.

Exogenous filtration markers have previously been used in ICU. Erley and colleagues used the SBI technique (5), but this method cannot be used for monitoring changing GFR during AKI. Salmon-Gandonneire and colleagues (6) observed a close correlation between a single Cl_P after SBI, measured over 12h, and mean Cl_R estimated on 4 separate occasions over the subsequent 24h. These findings are inconsistent with our data: we have demonstrated that a prolonged duration of infusion is required before a close agreement between Cl_P and Cl_R is observed (Figure 1). Caution needs to be applied when interpreting GFR measurements in AKI that are solely based upon Cl_P or SBI methods.

Inulin (7) and EDTA (8) infusions have been used for 4h (7), however, inulin is in short supply with increased manufacturing costs (27) and EDTA has risks associated with radiation exposure. Neither have been tested with prolonged infusions.

Iohexol has many properties of an “ideal marker” of filtration (28): it undergoes minimal protein-binding, almost all is filtered at the glomerulus, it undergoes no renal tubular reabsorption or secretion, it diffuses rapidly into extracellular spaces, and has an excellent safety profile (29). Highly reproducible laboratory results with low inter- and intra-patient CV are observed when Iohexol is measured by LC-MSMS (30). LC-MSMS measurements of Iohexol concentration are more accurate than routine laboratory SCr measurements (30). Iohexol is widely available and is 5-10% the cost of Inulin and 15% the cost of measuring GFR with Inulin.

Limitations

The CKD-EPI equation was used to estimate baseline GFR, rather than measured GFR. Measuring GFR in elective patients was not possible due to the logistics of being a specialist centre and the distances patients have to travel. However, CKD-EPI is an established method in stable patients (14).

Wider differences between Cl_P and Cl_R were observed when measured at lower GFR. This may suggest an increased role for $Cl_{NON-RENAL}$ or that these were sicker patients with greater changes in V_d . Agreement between Cl_R and Cl_P improved at later stages of infusion, suggesting a longer time is needed for redistribution between extracellular spaces in critically unwell patients than in our previously studied patients with stable GFR (9). Despite this, a good agreement between Cl_R and Cl_P was observed, particularly in later stages of the study.

Continuous infusions are too cumbersome for daily clinical practice but could be a useful research tool. CILDI offers a method of measuring changing GFR in AKI in clinical trials (e.g. comparing biomarkers with accurately measured GFR, measuring the effects of AKI on pathophysiological processes (31)).

Older radio-contrast agents have been associated with AKI (32), although this relationship may not be causative (33-37). AKI occurring after contrast administration is likely to be multi-factorial and may be more attributable to the underlying illness than radio-contrast. A threshold ratio of radio-contrast volume to weight and baseline eGFR has been suggested before contrast-associated AKI develops (38). By keeping the infused volume low this risk is minimised. In our method, infusion for > 6 days would be required before this threshold was exceeded in an anuric 40Kg patient. Alternatively, SBI methods (5,6) would require repeated administration of larger volumes of Iohexol and the threshold for toxicity would be exceeded sooner. The debate surrounding contrast-associated AKI remains

unresolved; a delayed nephrogram may be considered in patients with known low, or rapidly-declining, GFR.

Next stages:

The method was developed primarily for research purposes but it does provide opportunity to describe AKI more accurately and to assess more clinically-applicable methods. This, in turn, will allow clinicians to understand AKI in more detail. Biomarkers may be assessed more precisely and a definition of AKI better formulated: some biomarkers may be better than we realise. Improving AKI definitions will allow treatments to be tested accurately and could provide guidance on when to commence RRT. Early initiation of RRT may have survival advantages (39). In research, CILDI could improve investigation of biomarkers, of pathophysiology (31), and mechanisms of AKI.

Although CILDI defines AKI as GFR reduction of >10.3%, it is unclear whether symptoms manifest at this level of change, whether the rate of reduction in GFR is responsible for associated effects, or if a critical reduced GFR must be reached. Further research in this area is required, however, CILDI allows tracking of AKI and can help answer these questions. Furthermore, greater numbers are needed to determine whether small changes in GFR measured by CILDI have measurable differences in outcomes when compared with SCr.

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TABLE AND FIGURES

Figure 1. Change in plasma (Cl_P) and renal clearance (Cl_R) of Iohexol throughout the duration of the study. The top graph shows Cl_P and Cl_R as described by non-linear models, adjusted for baseline creatinine (SCr) and baseline eGFR by clinical group. The descriptions are made for an average baseline SCr of 72 μ mol/L and baseline eGFR of 82mL/min/1.73m² within the first 60h of the infusion. The bottom row shows Bland Altman agreement of plasma and renal clearance of CILDI at 14h and 48h of the study. The difference reduces with increasing infusion duration. At 14h bias of Cl_P is 9.9 $\pm$ 21.6/mL/min/1.73m², with 95% Limits of agreement (LoA) -32.5 to 52.3mL/min/1.73m²; this improves to -0.1 $\pm$ 3.6 mL/min/1.73m², LoA -7.2 to 7.1mL/min/1.73m² at 48h.

Subjects	Age (years)	Sex	BSA (m ²)	Baseline eGFR (mL/min/1.73m ²)	APACHE-II
<i>Nephrectomy group (n = 10)</i>					
MEDIAN	70	8M 2F	1.90	88.3	10.5
(IQR)	(54-77)		(1.81-2.12)	(67.6-97.4)	(7.5-15.0)
<i>Surgery group (n = 11)</i>					
MEDIAN	73	8M 3F	1.86	69.1	13.0
(IQR)	(61-79)		(1.72-2.01)	(50.6-86.0)	(13.0-14.0)
<i>KDIGO AKI criteria group (n = 13)</i>					
MEDIAN	71	8M 5F	1.98	96.7	16.0
(IQR)	(54-83)		(1.82-2.00)	(71.8-109.8)	(14.5-23.0)

Table 1: Demographic features of study subjects. Variables expressed as median and interquartile range (IQR). eGFR = estimated glomerular filtration rate (CKD-EPI equation); BSA = body surface area (15); APACHE = acute physiology and chronic health evaluation 2 score. This table is expanded further in the Supplementary Tables 1 and 2.

Values	Nephrectomy Group	Surgery Group	AKI Group
Baseline Values			
Mean SCr $\pm$ SD (μ mol/L)	83.0 $\pm$ 29.9	93.3 $\pm$ 24.0	65.5 $\pm$ 22.7
Mean eGFR $\pm$ SD [mL/min/1.73m ²]	[84.4 $\pm$ 27.1]	[69.1 $\pm$ 20.6]	[92.2 $\pm$ 23.3]
Values at 24 hours			
Mean PCr $\pm$ SD (μ mol/L) [%baseline] (mean = $\pm$ SD)	108.8 $\pm$ 38.5 [132.7 $\pm$ 17.5]	123.0 $\pm$ 91.1 [122.3 $\pm$ 59.3]	149.8 $\pm$ 71.0 [221.0 $\pm$ 68.8]
AKI stage (KDIGO)			
(0)	5	7	0
(1)	5	3	3
(2)	0	1	8
(3)	0	0	2
Cl_P (mL/min/1.73m ²) [% baseline eGFR] (mean = $\pm$ SD)	62.1 $\pm$ 19.0 [85.7 $\pm$ 30.2]	64.0 $\pm$ 27.5 [92.2 $\pm$ 27.4]	55.8 $\pm$ 28.9 [58.8 $\pm$ 20.6]
Cl_R (mL/min/1.73m ²) [% baseline eGFR] (mean = $\pm$ SD)	42.0 $\pm$ 17.8 [49.2 $\pm$ 11.0]	58.1 $\pm$ 40.5 [78.6 $\pm$ 40.3]	52.8 $\pm$ 35.6 [53.7 $\pm$ 32.3]
24 hour Fluid balance(L) (median, IQR)	0.32 (-1.12, 0.41)	-0.07 (-0.95, 1.16)	1.49 (0.92, 2.73)

Table 2: Plasma clearance (Cl_P) and Renal clearance (Cl_R) of iohexol at 24h. The worst AKI-KDIGO parameter (i.e. urine output or plasma creatinine (PCr) rise) was used in all groups. The AKI stage at 24h is listed, with the number of individuals within that group reaching each stage in parentheses. This table is expanded further in Supplementary Tables 3 and 4. Group population variances of Cl_P and Cl_R against time are provided in Supplementary Figures 1 and 2. Individual examples of how plasma iohexol concentration resulted in different Cl_P are provided in Supplementary Figures 7 and 8. SCr = serum creatinine, eGFR = estimated glomerular filtration rate, Cl_P = plasma clearance of iohexol, Cl_R = renal clearance of iohexol

Clearance	Bias (%)	SD (%)	Limits of agreement (%)
<i>Iohexol Cl_R vs 1hCrCl</i>			
Nephrectomy group	-3.4	16.6	-35.9 to +29.6
Surgery group	-15.7	22.9	-60.6 to +29.3
KDIGO-AKI group	-0.8	26.3	-52.3 to +50.6
Overall	-5.6	24.0	-52.6 to +41.5
<i>Iohexol Cl_R vs 4hCrCl</i>			
Nephrectomy group	-4.7	38.0	-79.1 to +70.0
Surgery group	-46.4	61.4	-166.6 to +73.9
KDIGO-AKI group	+5.1	54.7	-102.0 to +112.7
Overall	-11.4	56.7	-122.6 to +99.1
<i>Iohexol Cl_P vs 1hCrCl</i>			
Nephrectomy group	+9.5	29.5	-48.4 to +67.4
Surgery group	+33.2	37.7	-40.7 to +107.0
KDIGO-AKI group	+6.8	33.8	-42.6 to +73.0
Overall	+9.1	34.3	-58.1 to +76.3
<i>Iohexol Cl_P vs 4hCrCl</i>			
Nephrectomy group	+5.6	36.9	-66.7 to +77.9
Surgery group	-41.7	66.2	-171.3 to +88.2
KDIGO-AKI group	-0.7	43.1	-85.1 to +83.8
Overall	+7.9	38.7	-68.5 to +83.3
<i>1hCrCl vs 4hCrCl</i>			
Nephrectomy group	+0.05	34.9	-68.3 to +83.4
Surgery group	-31.5	53.4	-136.1 to 73.1
KDIGO-AKI group	-4.8	54.5	-111.6 to +102.1
Overall	-6.4	66.0	-93.0 to +165.9

Table 3. Iohexol Renal clearance (Cl_R) or plasma clearance (Cl_P) vs 1h-creatinine clearance ($CrCl$) and 4h-CrCl at 14h. Bland Altman agreement is shown.

Group	KDIGO AKI criteria	CILDI AKI criteria (>10.3% loss of GFR)	CILDI: >50% loss of GFR	
Nephrectomy (<i>n</i> = 10)	5	10	7	
Surgery (<i>n</i> = 11)	4	8	7	
KDIGO AKI (<i>n</i> = 13)	13	11	10	
Overall outcomes				
<i>n</i>	<i>Kpos/Cpos</i> 19	<i>Kpos/Cneg</i> 3	<i>Kneg/Cpos</i> 9	<i>Kneg/Cneg</i> 3
Outcome at 1 year				
Death	4	0	0	0
CKD ^a	14 ^b	0	8	1
Length of stay				
ICU median days (IQR)	4 (2.25-5.75)	5 (3.25-5.75)	2 (2-4.5)	2 (2-2)
Hospital median days (IQR)	20 (8-36)	11 (7.25-13.75)	6 (5-7)	6 (6-6.5)

Table 4: Comparison of AKI criteria in each group. Measurements were made at 24h. CILDI identified an additional 5 patients with AKI in the Nephrectomy group and 4 in the Surgery group. A further 3 subjects with KDIGO-AKI (*Kpos*) did not have AKI when measured by CILDI (*Cneg*). The following outcomes at 1 year are listed: death, progression to CKD, length of stay in hospital and ICU. No patients required renal replacement therapy (RRT) 1 year later. *Kpos* = positive for KDIGO-AKI criteria; *Kneg* = negative for KDIGO-AKI criteria; *CPos* = Positive for CILDI AKI criteria; *Cneg* = negative for CILDI AKI criteria; RRT = renal replacement therapy; CKD = chronic kidney disease ^adefined as either new CKD-EPI stages 2-5, or worsened stage if pre-existing CKD-EPI stages 2-5. ^bThis does not include the 4 patients who died; IQR = inter-quartile range.

SUPPLEMENTARY METHODS

COMPLETE METHODS

Study registration and ethical approval

The UK Clinical Research Network (<http://public.ukcrn.org.uk/>) adopted the study (Reference: 13391). Ethical approval was obtained from Queen's Square research ethics committee (reference: 12/LO/1179), which specialised in studies involving patients lacking capacity to consent. The Declaration of Helsinki (2008) (1) was adhered to throughout.

Patients

The study took place in an adult general intensive care unit. Three patient groups were selected: 1) *Nephrectomy*: Patients due an elective nephrectomy and thus a predictable reduction in GFR of approximately 50% (*defined onset of injury; predictable outcome*). 2) *Surgery*: Patients due elective major vascular surgery. These patients have a high risk of post-operative AKI (2) (*defined onset of injury; unpredictable outcome*). 3) *AKI*: Emergency patients admitted to ICU meeting Kidney Disease: Improved Global Outcomes (KDIGO) AKI criteria (3) (*unpredictable onset of injury; unpredictable outcome*).

Inclusions

- Patients over 18 years due an elective nephrectomy or major vascular surgery admitted to intensive care post-operatively, or
- Patients meeting KDIGO-AKI criteria (urine output or SCr) in ICU (3).
- Patients were only included if they had a pre-existing multi-lumen CVC and arterial catheter because this study was observational and was designed not to interfere with clinical care.

Exclusions

Inability to provide informed consent prior to elective surgery; allergy to radio-contrast media; CKD stage 5 or dialysis; patients taking drugs which could potentially interact with Iohexol (metformin if SCr > 150µmol/L, phenothiazines, mono-amine oxidase inhibitors, levo-thyroxine, amiodarone, interleukin-2 agents, Tc99m-MDP); disorders in which Iohexol may potentially interfere with monitoring (thyroid disease, myasthenia gravis phaeochromocytoma); hyperviscosity disorders (sickle cell disease, homocystinuria, multiple myeloma); pregnancy or breast-feeding.

Iohexol administration and sampling

Iohexol was administered via a central venous catheter with a one-way valve to prevent backflow. The giving set and syringe containing Iohexol were covered in a light-impermeable sheath (4). A loading dose (LD) was administered over 2 minutes (5) and followed by a continuous infusion of Iohexol (Omnipaque 300®) at 0.5mL/h (343.5mg/h) for up to 80h via Agila MC Injectomat pumps (6).

LD was calculated according to the formula:

$$LD = \text{Volume of distribution (Vd)} / \text{target steady state concentration (C}_{ss}\text{)}.$$

From the Summary of product characteristics (4, $Vd = 0.165\text{L/Kg}$ (95%CI: 0.108–0.219)*weight(Kg). The target C_{ss} ($100\mu\text{mol/L} = 0.1269\text{mL}$) is approximately 100 times the lower limit of quantitation by LC-MSMS, although the actual Iohexol concentration reached in individuals varied according to their GFR and Vd . The LD would have ideally been calculated using GFR, however, weight was used so that CILDI could be used in patients with

an unknown baseline GFR. In practice, LD varied between 1.12mL for the lightest subject (53.6Kg) and 2.76mL for the heaviest subject (131.8Kg) in our study. This is lower than the volume that would be required for each bolus if the single bolus method was used. For example, a previous study in critical care has used 0.1-0.4mL/Kg (7) on each occasion GFR was measured; this is equivalent to between 13.1 and 52.7mL for our largest patient. The volumes used in routine radio-contrast computed tomography scans are usually in the range of 70-150mL.

Plasma samples (0.5mL) were taken for Cl_P at 30 mins, 1h, 2h and 4h on day 0, and at 08:00h, 10:00h, 18:00h and 20:00h on days 1-3 from an arterial catheter. Urine samples were taken for Cl_R between plasma samples on day 0 and between subsequent morning plasma samples and evening plasma samples. Time zero was considered to be the time of commencing the infusion. Infusions were commenced within 1 hour of surgery in *Surgery* and *Nephrectomy* groups.

Laboratory procedures: Plasma samples were centrifuged at 3500rpm, at 4°C for 10 mins, with the supernatant stored at -80°C. Urine samples were also stored at -80°C immediately following collection. Once in the laboratory, particulate matter was separated by defrosting the frozen samples at 4°C and centrifuging at 1500rpm (4°C) for 4 minutes. Serum was decanted into 10µL aliquots. Fifty microliters of stabilising fluid were added to each aliquot. The constituents of the stabilising fluid were: 10mL de-ionised water, 250µL D₅-Iohexol, 25µL D₃-Creatinine, 25µL D₆-asymmetrical dimethylarginine, and 1.5µL symmetrical dimethylarginine. The mixture was precipitated by adding 200µL 1% (vol/vol) acetonitrile (Rathburn Chemicals Ltd., Walkerburn, Peebleshire, UK), and was then centrifuged at 20,000rpm for 3 minutes at 4°C. Two hundred microliters of the mixture were transferred

into a 96-well polypropylene well plate and analysed by the API 5000LC/ msms with QJET Ion guide accelerated by LINAC® collision cell (AB Applied Biosystems MDS SCIEX). Three quality controls were used with known plasma concentrations of Iohexol (10.6µmol/L, 516.0µmol/L, and 99.2µmol/L). Precision of laboratory specimens was determined by calculating mean coefficient of variation (CV) of all samples taken within 2-hour periods.

Glomerular Filtration Rate (GFR) calculation

Baseline estimated GFR (eGFR) was obtained from admission eGFR (CKD-EPI (8)) for elective patients or from hospital notes, if within the last 6 months. Cl_P was calculated by the formula: $Cl_P \text{ (mL/min)} = [\text{Iohexol infusion rate (}\mu\text{mol/min)}] / [\text{plasma Iohexol concentration (}\mu\text{mol/mL)}]$, adjusting for body surface area (BSA) (8). Cl_R was calculated by the formula: $Cl_R \text{ (mL/min)} = [U \times V] / P$, where U =urine Iohexol concentration (µmol/L), V = volume of urine (mL) per unit time (min), and P = mid-time point plasma Iohexol concentration (µmol/L), adjusting for (BSA) (9).

Comparison with KDIGO and outcomes

GFR measurements were compared with KDIGO-AKI criteria (3) and classified according to whether subjects met KDIGO and CILDI criteria for AKI: KDIGO-positive (K_{pos}), KDIGO-negative (K_{neg}), CILDI-positive (C_{pos}), CILDI-negative (C_{neg}). Length of stay in ICU and in hospital, development of CKD within 1 year, need for renal replacement therapy (RRT), and death were also recorded. CILDI-AKI criteria was defined as GFR loss >10.3% (9). We also recorded the number of patients with 50% loss in GFR measured by CILDI, to compare with KDIGO-AKI stage 2.

Statistical methods

- a) Demographic data: Data for age, sex, body surface area, baseline eGFR and APACHE-II scores were collected and variables were expressed as median and interquartile range.
- b) SCr , Cl_P , Cl_R compared with baseline SCr and eGFR: multiple measurements per individual in a time-ordered manner creates a longitudinal structure to the data with two levels of variability: between subjects (*inter-subject*) and within subjects (*intra-subject*). A mixed model with unstructured variance-covariance matrix was used to estimate the inter-subject average behaviour through time, with models accounting for the unbalanced sets of outcome measurements. This model also accounts for the intra-subject variability of each individual's curve whilst a "grand mean curve" is estimated, adjusted for the effects of other variables on each outcome. These models explain how Cl_R , Cl_P , $CrCl$ behave through time, adjusted by clinical group and baseline SCr and baseline eGFR. All outcomes underwent one-to-one logarithmic transformation, to reduce their range and variability without altering the qualitative aspects of the results.
- c) Expected change: The expected 50% change longitudinally was assessed by comparing logarithmic conversion of measured Cl_P and Cl_R with time, when using baseline mean eGFR as a comparator: a change in log value of approximately 0.7 was expected.
- d) Level of agreement between Cl_P and Cl_R , $CrCl$ -1, and $CrCl$ -4 was assessed at specific time-points using Bland-Altman agreement (10). Data were shown as absolute differences (in mL/min/1.73m²).

- e) Outcomes: incidence of development of new CKD or progression of pre-existing CKD, RRT and death were assessed. Mean length of stay in ICU or hospital was also assessed.

Graphpad Prism®, version 7.00 (Graphpad software, Inc.) was used for statistical analysis.

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SUPPLEMENTARY TABLE 1

Subject	Age (years)	Sex	BSA (m ²)	Diagnosis	Baseline eGFR (mL/min/1.73m ²)	APACHE-II
<i>Nephrectomy group</i>						
1	82	M	1.90	RCC	39.7	6
2	44	F	2.08	RCC	129.3	8
3	77	M	1.89	RCC	85.0	15
4	71	M	1.67	RCC	94.9	12
5	81	M	1.73	RCC	50.1	16
6	46	M	1.82	RCC	91.6	8
7	76	M	1.81	RCC	84.2	12
8	69	M	2.66	RCC	62.1	15
9	53	F	2.40	RCC	108.3	5
10	58	M	2.14	RCC	98.9	9
MEDIAN (IQR)	70 (54-77)		1.90 (1.81-2.12)		88.3 (67.6-97.4)	10.5 (7.5-15.0)
<i>Vascular Surgery group</i>						
11	51	M	2.04	ABB	88.4	13
12	58	M	2.34	Carotid-bypass	98.3	9
13	79	F	1.86	EVAR	49.7	13
14	72	M	1.75	TEVAR	69.5	16
15	82	M	1.95	EVAR	83.5	13
16	59	F	1.78	TEVAR repair	99.2	9
17	73	M	1.98	TEVAR	72.7	13
18	82	M	1.53	EVAR	52.4	14
19	78	F	1.48	EVAR + renal bridge	50.7	13
20	74	M	1.70	Embolectomy	45.0	16
21	63	M	2.05	Open AAA repair	51.0	14
MEDIAN (IQR)	73 (61-79)		1.86 (1.72-2.01)		69.1 (50.5-86.0)	13.0 (13.0-14.0)
<i>KDIGO AKI criteria group</i>						
22	83	F	1.46	SBO	106.6	22
23	73	F	1.67	Pneumonia	88.9	11
24	61	M	2.33	Pneumonia	98.6 ^a	20
25	91	M	1.56	CCF	58.6	14
26	72	F	2.39	sepsis	75.9	15
27	42	M	1.99	ALD	108.1	18
28	62	M	1.94	sepsis	96.1	15
29	71	M	1.98	Neutropaenic sepsis	122.9	24
30	54	M	2.03	Urosepsis	116.8	11
31	92	M	1.82	sepsis	54.7	25
32	90	F	2.00	Pneumonia	59.5	16
33	51	F	1.83	Duodenal ulcer	114.9	15
34	54	M	2.00	SBO	97.3	26
MEDIAN (IQR)	71 (54-83)		1.98 (1.82-2.00)		96.7 (71.8-109.8)	16.0 (14.5-23.0)

Supplementary Table 1: Demographic features of study subjects. Variables are expressed as median and interquartile range (IQR). eGFR = estimated glomerular filtration rate (CKD-EPI equation); APACHE = acute physiology and chronic health evaluation 2 score; RCC = renal cell

carcinoma; EVAR = endovascular aortic aneurysm repair; TEVAR = Thoracic endovascular aortic aneurysm repair; ABB = aorto-bifemoral bypass; AAA = abdominal aortic aneurysm repair; SBO = small bowel obstruction; CCF = congestive cardiac failure; ALD = alcoholic liver disease. ^aunknown baseline: eGFR taken from lowest creatinine on admission. The co-morbidities are described in Supplementary Table 2.

SUPPLEMENTARY TABLE 2

Group	CVS	Resp	Renal	GI/Liver	Neuro	Onc	Haem	Endo	Rheum
Nephrectomy	7	0	1	1	1	10	2	1	0
Surgery	9	8	3	1	1	1	0	2	1
AKI	7	2	2	4	2	2	4	1	2

Supplementary Table 2: Co-morbidities according to group. CVS = cardiovascular (ischaemic heart disease or hypertension, but not peripheral vascular disease); resp = respiratory (Emphysema with FEV1<60%, severe asthma, bronchiectasis); GI/Liver = gastrointestinal (inflammatory bowel disease, liver cirrhosis, fatty liver disease); Neuro = neurological (stroke, Parkinson's disease); Onc = Oncological disease (renal cell cancer, lung cancer, bowel cancer); Haem = Haematological disorder (chronic anaemia of known cause); Endo = endocrine disease (diabetes mellitus, hypothyroidism); Rheum = rheumatological disease (rheumatoid arthritis, connective tissue disease, osteoarthritis).

SUPPLEMENTARY TABLE 3

Subject	Baseline SCr ($\mu\text{mol/L}$) eGFR [mL/min/1.73m ²]	Mean PCr ($\mu\text{mol/L}$) [%baseline]	AKI stage (KDIGO)	Cl_P (mL/min/1.73m ²) [% baseline eGFR]	Cl_R (mL/min/1.73m ²) [% baseline eGFR]	Fluid Balance (mL)
<i>Nephrectomy group</i>						
1	141 [39.7]	195 [138]	1 ^a	59.3 [149]	22.5 [57] ^c	-1600
2	52 [129.3]	78 [150]	1	98.0 [75]	80.9 [63]	+385
3	73 [85.0]	87 [119]	1 ^b	68.0 [80]	33.0 [39]	+412
4	62 [94.9]	70 [113]	1 ^b	61.8 [65]	42.1 [44]	+1970
5	117 [50.1]	132 [113]	0	37.2 [74]	32.8 [65]	-486
6	87 [91.6]	112 [129]	0	72.9 [86]	63.6 [69]	-3179
7	76 [84.2]	100 [132]	0	57.7 [69]	42.9 [51]	+365
8	105 [62.1]	130 [124]	0	49.6 [80]	32.0 [52]	-1335
9	47 [108.3]	66 [140]	0	97.6 [89]	58.1 [54]	+281
10	70 [98.9]	118 [169]	1	63.3 [64]	36.1 [37]	+2338
MEAN $\pm$ SD	83.0 $\pm$ 29.9 [84.4 $\pm$ 27.1]	108.8 $\pm$ 38.5 [132.7 $\pm$ 17.5]		62.1 $\pm$ 19.0 [85.7 $\pm$ 30.2]	42.0 $\pm$ 17.8 [49.2 $\pm$ 11.0]	-84.9 $\pm$ 1649.6
<i>Surgery group</i>						
11	87 [88.4]	106 [122]	1 ^b	64.0 [72]	127.1 [144] ^c	+415
12	71 [98.3]	71 [100]	0	96.0 [98]	122.7 [125] ^c	-70
13	94 [49.7]	105 [112]	0	40.7 [82]	24.9 [50]	-1284
14	94 [69.5]	108 [115]	0	42.4 [61]	23.7 [34]	+1364
15	70 [83.5]	62 [89]	0	89.2 [107]	73.0 [87] ^c	+951
16	54 [99.2]	37 [69]	0	118.0 [119]	90.9 [92] ^c	-467
17	90 [72.7]	98 [109]	0	58.8 [81]	44.9 [62]	+1679
18	112 [52.4]	147 [131]	1 ^a	45.1 [86]	33.7 [64]	+2003
19	93 [50.7]	69 [74]	0	68.3 [135]	35.5 [70] ^c	-619
20	133 [45.0]	180 [135]	1 ^a	56.9 [126]	55.3 [123] ^c	-2599
21	128 [51.0]	370 [289]	2	24.7 [48]	6.8 [13]	-3562
MEAN $\pm$ SD	93.3 $\pm$ 24.0 [69.1 $\pm$ 20.6]	123.0 $\pm$ 91.1 [122.3 $\pm$ 59.3]		64.0 $\pm$ 27.5 [92.2 $\pm$ 27.4]	58.1 $\pm$ 40.5 [78.6 $\pm$ 40.3]	-199.0 $\pm$ 1761.5
<i>KDIGO-AKI group</i>						
22	26 [106.6]	39 [150]	1	105.0 [99]	102.3 [96]	+2731
23	68 [88.9]	78 [115]	1 ^b	58.3 [66]	50.4 [57]	+1450
24	67 [98.6]	217 [324]	3	36.7 [37]	33.5 [34]	+541
25	97 [58.6]	196 [202]	2	33.1 [56]	31.5 [54]	+1489
26	69 [75.9]	139 [201]	2	45.8 [60]	78.7 [104]	+1550
27	74 [108.1]	202 [273]	2	39.5 [37]	40.5 [37]	+2438
28	70 [96.1]	207 [296]	2	36.0 [37]	23.0 [24]	+1407
29	33 [122.9]	37 [112]	1 ^b	101.2 [82]	107.7 [88]	+459
30	50 [116.8]	102 [204]	2	102.5 [88]	101.5 [87]	+3358
31	102 [54.2]	234 [229]	2	33.7 [62]	8.7 [16]	+5808
32	76 [59.5]	227 [299]	3 ^b	21.7 [36]	0.5 [0.1]	+5370
33	41 [114.9]	105 [256]	2	60.4 [53]	63.6 [55]	+435
34	78 [97.3]	165 [212]	2	50.9 [52]	45.0 [46]	+923
MEAN $\pm$ SD	65.5 $\pm$ 22.7 [92.2 $\pm$ 23.3]	149.8 $\pm$ 71.0 [221.0 $\pm$ 68.8]		55.8 $\pm$ 28.9 [58.8 $\pm$ 20.6]	52.8 $\pm$ 35.6 [53.7 $\pm$ 32.3]	+2535.3 $\pm$ 555.6

Supplementary Table 3: Plasma clearance (Cl_P) and Renal clearance (Cl_R) of Iohexol at 24h.

The worst AKI-KDIGO parameter (i.e. urine output or plasma creatinine (PCr) rise) was used

in all groups. The AKI parameter used is percentage increase in PCr, unless stated (PCr >26 μ mol/L^a; urine output^b). P value (t test) is of the difference between Cl_P and Cl_R . Mean peak Cl_R in patients receiving Dopexamine^c was 132.1 $\pm$ 20.0% of baseline eGFR. Patients receiving Dopexamine are discussed further in the additional results section. Subjects 20, 22 and 26 did not have AKI when defined by CILDI.

SUPPLEMENTARY DATA TABLE 4

	AUGMENTED Cl_R	NOT AUGMENTED Cl_R
Dopexamine	5	2
No dopexamine	0	26

Supplementary Table 4: Comparison of renal clearance (Cl_R) of Iohexol in subjects receiving Dopexamine with those not receiving Dopexamine. Augmented Cl_R (ARC) was defined as Cl_R >130% of baseline eGFR (11). Seven subjects were given Dopexamine as part of a routine post-operative ICU protocol. Five (4 from Surgery group, 1 from Nephrectomy group) developed ARC while receiving Dopexamine. Mean peak Cl_R at 24h in patients receiving Dopexamine was $132.1 \pm 20.0\%$ of baseline eGFR. None of the subjects who were not given Dopexamine developed ARC (Fisher's exact test $P < 0.0001$). Dopexamine was stopped in all patients within 8h, although GFR remained elevated for up to 24h. Our data are too small to make firm conclusions as to whether this phenomenon is due to the inotropic effects of Dopexamine, an "ARC" as a compensatory response to critical illness, or a peculiar effect of Dopexamine.

Supplementary Figure 1: The effect of time on plasma clearance (Cl_p) of Iohexol. Figures are presented as logarithmic transformation of Cl_p and are adjusted for baseline creatinine (SCr) and baseline eGFR by clinical groups. The predictions and their uncertainties (thick lines) are made for a patient with average level of baseline SCr of $72\mu\text{mol/L}$ and baseline level of eGFR 82mL/min/1.73m^2 .

Supplementary Figure 2: The effect of time on renal clearance (Cl_R) of Iohexol. Figures are presented as logarithmic transformation of Cl_R and are adjusted for baseline creatinine (SCr) and baseline eGFR by clinical groups. The predictions and their uncertainties (thick lines) are made for a patient with average level of baseline SCr of $72\mu\text{mol/L}$ and baseline level of eGFR 82mL/min/1.73m^2 .

Supplementary Figure 3: Predicted renal clearance (Cl_R) of Iohexol up to 24h only and baseline eGFR. Figures are represented as logarithmic transformation of GFR. The dots represent individual baseline eGFR at time 0, and the solid lines represent the expected group mean Cl_R with the dashed lines representing 95% confidence intervals. The predicted log-transformed means of eGFR are: Nephrectomy group =4.381137; Surgery group =4.195352; AKI group =4.4906. A 50% reduction in baseline eGFR translates into a difference between log values of approximately 0.7 between log baseline eGFR and predicted Cl_R .