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Exposure to Contrast Media in the peri-operative period confers no additional risk of AKI in surgical patients

Ian Zealley[1]

Huan Wang[2]

Peter T. Donnan[2]

Samira Bell[2,3]

[1]Department of Radiology, Ninewells Hospital, Dundee, UK.

[2]Population Health Sciences, University of Dundee, Dundee, UK.

[3]Renal Unit, Ninewells Hospital, Dundee, UK.

Corresponding Author:

Samira Bell
Renal Unit
Ninewells Hospital
Dundee
DD1 9SY

Tel: 00 44 1382 633913
Fax: 00 44 1382 632327

E-mail: samira.bell@nhs.net

Key words: acute kidney injury, contrast, epidemiology, peri-operative

Abstract

Background

Iodinated contrast media used in angiography and computed tomography (CT) scans is an important cause of AKI in hospitalized patients undergoing surgery. Contrast induced nephropathy leads to AKI soon after contrast media administration. The aim of the study was to determine whether the timing of contrast media exposure related to diagnostic imaging during the immediate peri-operative period influences the risk of post-operative AKI.

Methods

All patients aged 18 or over who underwent diagnostic imaging within 7 days of non-cardiac surgery between the1st of January 2003 and 31st of December 2013 in the Tayside region of Scotland, UK were included in the analysis. The primary outcome of AKI was defined using the KDIGO creatinine based criteria. Multiple logistic regression was performed to identify predictors for AKI.

Results

Of 9,300 patients, 6,224 were exposed to CM in the immediate peri-operative period and 3,076 were not. Post-operative AKI occurred in 678 (10.9%) of the 6,224 patients who were exposed to CM. On multiple logistic regression, independent predictors of post-operative AKI were increasing age, male gender, lower baseline renal function and treatment with ACE inhibitors or ARB. Timing of CM exposure did not affect risk of developing AKI, OR 0.972 (95% CI 0.935 - 1.010), p=0.146.

Conclusions

For patients who have either just had or are soon to undergo general surgical procedures there appears to be no need to limit CT scan quality by avoiding the administration of contrast media. These patients may benefit from the increased diagnostic utility of contrast-enhanced CT scans without increasing their risk of peri-operative AKI.

Introduction

Acute Kidney Injury (AKI) affects 1 in 5 people hospitalized patients with a significant proportion of cases estimated to be preventable[1]. It is associated with increased mortality of up to 50% in severe AKI, but even mild, transient AKI is associated with both increased long term mortality and the future development of chronic kidney disease (CKD)[2, 3].

For many years it has been widely accepted that one of the leading causes of AKI in hospitalized patients is iodinated contrast media (CM) used in angiography and computed tomography (CT) scans [4], with contrast induced nephropathy (CIN) leading to AKI soon after CM administration. The risk of CIN is negligible in patients with normal renal function but the incidence appears to rise to as high as 25% in patients with pre-existing renal impairment or in the presence of risk factors such as CKD and diabetes, advanced age and use of certain concurrent medication. CIN is reported to be the third commonest cause of new AKI in hospitalized patients, after decreased renal perfusion and medication responsible for 11% of cases [5].

Another important cause of AKI in hospitalized patients is surgery. The incidence of AKI after surgery ranges from 18% to 47% and mortality from 1% to 30% depending on which AKI definitions are applied. Historically it was difficult to reliably establish the incidence of AKI due to the lack of a universally accepted definition. Using the now widely accepted Kidney Disease Improving Global Outcomes (KDIGO) criteria we have shown that rates of AKI rates ranged from 6% in orthopaedic surgery to 25% in vascular surgery[6] highlighting the extent of the current problem.

An apparently synergistic relationship between the “double hits” of surgery and CM exposure has been reported in cardiac surgery where operations often take place soon after angiography. The incidence of postoperative AKI is correspondingly high at 10-25% depending on presence of pre-existing renal impairment. A meta-analysis of studies has advocated that as long a gap as clinically feasible be allowed between the nephrotoxic insults of surgery and CM exposure [7]. This evidence presents a strong theoretical risk that

CM exposure and surgery are separate and complementary risk factors for AKI, and that modifying clinical practice by reducing CM exposure in the perioperative period may be a potentially effective target to reduce a potentially avoidable risk of AKI in the wider general surgical population.

The aim of our study was to determine whether the timing of contrast media exposure related to diagnostic imaging during the immediate peri-operative period influences the risk of post-operative AKI in the general surgical population.

Materials and Methods

Study Population

Adults aged 18 or above who underwent non-cardiac surgery and a diagnostic imaging investigation including the administration of CM within 7 days of the surgical procedure in a hospital in the Tayside region of Scotland from 1st January 2003 to 31st December 2013 were included in the study. Patients who were receiving chronic renal replacement therapy or had missing pre or post-operative creatinines were excluded.

Ethical Statement

Anonymised record linkage was conducted according to Health Informatics Centre , University of Dundee[8] Standard Operating Procedure. The Tayside Research Ethics Committee does not require submission of individual studies that follow this standard operating procedure which is Caldicott Guardian approved. The study manuscript has been prepared in adherence to the recommendations of the strengthening of the reporting of observational studies in epidemiology (STROBE) workshop[9].

Data Sources

Data were linked using the Health Informatics Centre (HIC) at the University of Dundee[8]HIC enables anonymized health record linkage for the population of Tayside (n=400,000) using a unique identifying Community Health Index (CHI) number. Data were linked between the following datasets: Scottish Morbidity Record of hospital admissions

(SMR01); laboratory results, medicines dispensed by community pharmacies, Scottish Index of Multiple Deprivation (SIMD), the Scottish Care Initiative-Diabetes Collaboration, the Scottish Renal Registry and the Healthcare Software Solutions Computerised Radiology Information System (HSS CRIS). SMR01 provides information on age, sex, postcode and admission and discharge dates and operation procedure codes. Creatinine measurements were obtained from the laboratory system. Deprivation category was obtained from Scottish Index of Multiple Deprivation and the Scottish Care Initiative-Diabetes Collaboration provided information on diabetes type and date of diagnosis. Patients receiving chronic dialysis or post renal transplant were identified using the Scottish Renal Registry. Diagnostic imaging investigations involving the administration of CM were identified from the HSS CRIS radiology system by their specific examination codes with data extracted on type and volume of CM administered.

Outcome

The outcome of interest was the development of any severity of AKI (Stages 1-3) during the first week post-operatively. AKI severity was defined using Kidney Disease Improving Global Outcomes Criteria[10]. These criteria were applied using serum creatinine at baseline (most recent prior to surgery within 6 months) as pre-operative measurement and maximal serum creatinine during the first seven after surgery days as post-operative measurement. Post-operative AKI was defined using the KDIGO criteria. Patients must have had at least stage 1 AKI, defined as a rise in serum creatinine of 26.5 µmol/l or more or a post-operative serum creatinine of greater than 150% of baseline serum creatinine, to be classified as having post-operative AKI[10].

Statistical Methods

Baseline characteristics were displayed as mean and standard deviation (SD) for continuous variables. Categorical variables were displayed as number and percentage. SIMD deprivation and days of CM exposure before surgery were displayed as number and

percentage for each category but were included into further analyses as continuous variables.

The cohort comprised of all patients who had undergone surgical procedures and radiological investigations involving the administration of CM in the Tayside region of Scotland. The index date of entry was the date of admission prior to the surgical procedure and the follow-up period was for 7 days. The primary outcome was AKI and was analysed using logistic regression with AKI as a binary outcome in the 7 days after surgery. Variables entered into the multiple logistic regression analysis were: age, gender, SIMD deprivation, baseline renal function, diabetes, prescription of ACE inhibitors or ARBs, prescription of HMG Co reductase inhibitors (statins), prescription of NSAIDs, prescription of loop diuretics and days of CM exposure before surgery. Baseline renal function was assessed using estimated glomerular filtration rate (eGFR), which was calculated using the CKD-EPI equation[11]. The rates were then categorised as less than 29, 30-44, 45-59 and greater than 60. Missing values of SIMD were imputed using multiple imputation[12]. Results are expressed as Odds Ratios (OR) and their 95% confidence intervals. In addition, ordinal logistic regression was carried out with the outcome as the three stages of AKI in order to assess whether any of the variables were associated with severity of AKI. Analyses were implemented in Statistical Analysis Software (SAS v9.3).

Results

Between the 1st Jan 2003 and 31st Dec 2013, 13,482 patients in the Tayside region of Scotland underwent surgery and also had diagnostic imaging investigations performed. Among the 13,482 patients, only 9,300 had SCr tested within 6 months before and 7 days after surgery. Of the 9,300 patients, 6,224 were exposed to CM in the immediate peri-operative period and 3,076 were not. Post-operative AKI occurred in 678 (10.9%) of the 6,224 patients who were exposed to CM. Of these 540 were Stage 1, 91 stage 2 and 47 Stage 3.

Baseline Demographics

Baseline characteristics of patients exposed to and not exposed to CM with and without AKI are shown in Table 1. Mean age was higer in those with AKI (71.2 SD 13.9) compared to those without AKI (64.8 SD 16.8). Baseline renal function was lower in those with AKI (median eGFR: 60 ml/min (IQR 40 - 83) compared to those without AKI (median eFGR: 80 ml/min (IQR: 59 - 97). Post-operative AKI occurred in 678 (10.9%) of the 6,300 patients who were exposed to CM and 329 (10.7%) of 3076 not exposed to contrast. Relative risk of developing AKI in the patients exposed to contrast media was 1.018 (95% CI 0.899 - 1.153).

Predictive Variables for AKI

Results from multiple logistic regression are shown in Table 2. After entering 10 variables into the multiple logistic regression model, independent predictors of post-operative AKI were increasing age, male gender, lower baseline renal function and treatment with Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Timing of CM exposure did not affect risk of developing AKI, OR 0.972 (95% CI 0.935 - 1.010), p=0.146.

Ordinal logistic regression for stages of post-operative AKI

Results of ordinal logistic regression with stage of AKI as the outcome are shown in Table 3. Only baseline renal function was significantly associated with the severity of post-operative AKI. The time in days btween use of CM and surgery exposure after adjustment for baseline renal function did not significantly impact the severity of post-operative AKI OR 0.907 (95% CI 0.823 - 1.000), p=0.051.

Discussion

We have demonstrated that exposure to CM appears to confer little or no additional risk of AKI in patients undergoing general surgical procedures. In contrast, several other well known risk factors for AKI such as male gender, baseline renal function, presence of diabetes and treatment with ACE inhibitors and ARBs remained strong predictors of AKI in this clinical setting .

Iodinated radiological CM are known to be nephrotoxic so it is perhaps surprising that this nephrotoxic effect does not appear to add appreciably to the risk of developing AKI in patients undergoing general surgical procedures. It seems unlikely that the nephrotoxic effect of CM are mitigated by the physiolological insults of surgery and the underlying medical conditions precipitating the need for surgery. It may be that the the physiological derangements related to the surgery and underlying patient co-morbidities play a greater role than the effect of exposure to CM. For this to be the case the additional nephrotoxic effect of CM exposure in this clinical setting must be small and, for all practical purposes, negligible for these patients.

A recent large study of almost 8 million hospitalised patients in 2009 in the United States showed that CM exposure was not associated with an increased risk of AKI. The authors concluded that the risk of CIN may be overstated in the literature and overestimated by clinicians [13]. An accompanying editorial suggested “it may be appropriate to moderately liberalize the overall use of contrast” whilst continuing to carefully weigh the potential benefits versus the risks of the procedure[14]. This study was however limited by the fact that AKI was defined using ICD-9 codes perhaps underestimating its incidence. Another large study reported that CM exposure in the absence of pre-existing CKD was not associated with increased risk of AKI[15] . A smaller study of 100 hospitalised patients with stable renal function found similarly that AKI following CM exposure was rare in the absence of confounding risk factors such as nephrotoxic medications and CKD[16] . Our findings that CM exposure did not add appreciably to the risk of AKI in patients undergoing surgery lends

support to the suggestion that the influence of CM exposure alone on the risk of AKI may be clinically insignificant where other risk factors are present.

The current study draws data from a twelve year time period during which both awareness of CIN and preventive measures have evolved. Although impossible to define numerically, during the study period, there has undoubtedly been increasing clinician awareness of CIN leading to the development of several collaborative “renal protection” protocols which appeared to be better adhered to than dictats emanating unilaterally from the department of radiology. Changes in information technology have also facilitated a more considered approach to patients with impaired renal function. These include improvements in the hospital information systems (HIS) allowing easier access to uptodate blood results and integration of HIS with the radiology information system (RIS). This allows the radiology department staff to view the most recent eGFR results for patients at the time of appointing radiological procedures. This facilitates discussion and management of patients with impaired renal function undergoing contrast enhhanced scans. Advance consideration of challenging cases would sometimes result in deferred radiological examinations, careful fluid management around the time of CM administration, or even alteration of investigation plans to utilise tests which avoid CM altogether.

A “renal protection” guideline was implemented in 2012 in Tayside. This recommended administering either 0.9% saline for 12 hours pre and post scan or 1.26% sodium bicarbonate for 1 hour pre and 6 hours post scan in high risk patients. Prior to 2012, there was no hospital wide guideline in place and so practice varied considerably. Contrast agents used during the study period included iopamidol, iopromide and iohexol. Iso-osmolar agents reported to be associated with reduced risk of renal impairment were employed in a very small number of patients (dozens) in the mid-2000s but this approach did not follow any planned protocol and was not recorded in any readily accessible database format[17].

Strengths of our study include the large cohort size and the use of the widely accepted KDIGO criteria to define AKI allowing inclusion of milder forms of AKI. However our study is limited by the use of routinely collected data preventing the inclusion of intra-operative factors, exact dose of contrast administration and in-patient prescribing which may influence risk of AKI. In addition our population was predominantly Caucasian and so our findings may not be applicable to other ethnicities. We were unable to use data on co-morbidities due to under reporting[18]. We therefore used number of prescribed medications prior to admission which has been shown to correlate well with co-morbidity[19].

CT scanning has become the workhorse imaging investigation in hospitalized patients with abdominal and cardiovascular disease[20, 21]. Although CT of the abdomen can be performed without intravenous CM, the use of CM facilitates good accuracy and a high level of diagnostic confidence [21]. Although radiology staff are generally aware of CIN and its risk factors it has been suggested that more could be done by radiologists and referring physicians to reduce the risk of CIN [22]. Anecdotally we are aware that radiologists often avoid administering intravenous CM during CT scanning of patients who are considered to be at risk of CIN, and again anecodotally we are aware that radiologists consider such CT scans to be of substantially poorer diagnostic utility than CT scans performed with intravenous CM.

An episode of AKI, even after biochemical resolution, is associated with long term consequences such as greater risk of readmission, development and progression of chronic kidney disease (CKD) and poorer long term survival. In addition to these adverse health outcomes, AKI has a significant economic impact. Increased costs are due to increased length of hospital in-patients stay, increased investigation, intensive care admission and renal replacement therapy (RRT). In the United Kingdom the cost of in-hospital AKI alone (not including AKI in the community) is estimated to be between £434 and £620 million per year [23].

In the field of cardiac surgery a strong relationship has been demonstrated between synchronous CM exposure and high CM volumes and an increased risk of postoperative AKI[7]. Dose-response type relationships have been demonstrated between the risk of AKI and (i) close timing of angiography and surgery [7] and (ii) the amount of CM administered[24]. A significant association has been identified between AKI and volume of CM exposure at endovascular aneurysm repair (EVAR), with a corresponding deleterious effect on in-hospital mortality[25].

This data is lacking in the field of non-cardiac surgery where the usual source of CM exposure is CT scanning. CM-enhanced CT scans are commonly performed on patients undergoing non-cardiac surgery in both the preoperative and postoperative periods. CM-enhanced CT scans and angiography are commonly performed in the immediate pre- and post-operative periods, especially in the more vulnerable group of patients undergoing emergency surgery.

Shorter intervals between contrast media exposure and surgery were not associated with an increase in the risk of post-operative AKI. However male gender, baseline renal function, presence of diabetes and treatment with ACE inhibitors and Angiotensin Receptor Blockers were significant predictors of post-operative AKI. For patients who have either just had or are soon to undergo general surgical procedures there appears to be no need to limit CT scan quality by avoiding the administration of contrast media. These patients may benefit from the increased diagnostic utility of contrast-enhanced CT scans without increasing their risk of perioperative AKI.

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Conflict of Interest Statement

IZ, YH and SB report no conflict of interest. PTD reports grants from Shire Pharmaceuticals, grants from Novo Nordisk, grants from GSK, grants from AstraZeneca, grants from Gilead, outside the submitted work; and Prof Donnan is a member of New Drugs Committee of the Scottish Medicines Consortium.

Authors' Contribution

SB, IZ conceived the study, interpreted the data and drafted the article. PTD interpreted the data and revsed the article. HW analysed the data and drafted and revised the article. All authors providing intellectual content of critical importance to the work described and approved of the final version.

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Table 1: Baseline characteristics of patients undergoing surgery and radiological investgations exposed and not exposed to CM with and without AKI

Characteristics	Exposure to contrast media (n = 6224)			Non-exposure to CM (n = 3076)		
	AKI (n=678)	No AKI	Overall	AKI (n=329)	No AKI	Overall
Mean (SD) age (years)	70.8 (14.5)	64.0 (17.0)	64.8 (16.9)	71.9 (12.4)	66.3 (16.2)	66.9 (15.9)
Gender (M:F)	376 (55.5%)	2774 (50.0%)	3150 (50.6%)	181 (55.0%)	1374 (50.0%)	1555 (50.6%)
SIMD deprivation category:						
1 (most deprived)	126 (18.6%)	1166 (21.0%)	1292 (20.8%)	85 (25.8%)	587 (21.4%)	672 (21.8%)
2	112 (16.5%)	988 (17.8%)	1100 (17.7%)	52 (15.8%)	497 (18.1%)	549 (17.8%)
3	105 (15.5%)	951 (17.1%)	1056 (17.0%)	51 (15.5%)	466 (17.0%)	517 (16.8%)
4	208 (30.7%)	1479 (26.7%)	1687 (27.1%)	103 (31.3%)	733 (26.7%)	836 (27.2%)
5 (lease deprived)	121 (17.8%)	865 (15.6%)	986 (15.8%)	33 (10.0%)	419 (15.3%)	452 (14.7%)
Missing	6 (0.9%)	97 (1.7%)	103 (1.7%)	5 (1.5%)	45 (1.6%)	50 (1.6%)
eGFR category (mL/min):						
<29	97 (14.3%)	225 (4.1%)	322 (5.2%)	38 (11.6%)	124 (4.5%)	162 (5.3%)
30-44	117 (17.3%)	375 (6.8%)	492 (7.9%)	53 (16.1%)	258 (9.4%)	311 (10.1%)
45-59	126 (18.6%)	672 (12.1%)	798 (12.8%)	64 (19.5%)	407 (14.8%)	471 (15.3%)
>60	338 (49.9%)	4274 (77.1%)	4612 (74.1%)	174 (52.9%)	1958 (71.3%)	2132 (69.3%)
Diabetes	144 (21.2%)	807 (14.6%)	951 (15.3%)	68 (20.7%)	399 (14.5%)	467 (15.2%)
No. receiving ACE inhibitors or ARBs	288 (42.5%)	1508 (27.2%)	1796 (28.9%)	154 (46.8%)	754 (27.4%)	908 (29.5%)
No. receiving NSAIDs	142 (20.9%)	1187 (21.4%)	1329 (21.4%)	62 (18.8%)	494 (18.0%)	556 (18.1%)
No. receiving statins	289 (42.6%)	1644 (29.6%)	1933 (31.1%)	137 (41.6%)	815 (29.7%)	952 (30.9%)
No. receiving loop diuretics	157 (23.2%)	813 (14.7%)	970 (15.6%)	89 (27.0%)	465 (16.9%)	554 (18.0%)
No. of prescribed drugs:						
None	19 (2.8%)	290 (5.2%)	309 (5.0%)	14 (4.3%)	180 (6.6%)	194 (6.3%)
1-5	110 (16.2%)	1482 (26.7%)	1592 (25.6%)	65 (19.8%)	734 (26.7%)	799 (26.0%)
6-10	222 (32.7%)	1590 (28.7%)	1812 (29.1%)	113 (34.3%)	853 (31.1%)	966 (31.4%)
11-15	162 (23.9%)	1123 (20.2%)	1285 (20.6%)	66 (20.1%)	517 (18.8%)	583 (19.0%)
16-20	94 (13.9%)	578 (10.4%)	672 (10.8%)	40 (12.2%)	294 (10.7%)	334 (10.9%)
>20	71 (10.5%)	483 (8.7%)	554 (8.9%)	31 (9.4%)	169 (6.2%)	200 (6.5%)
Timing of CM (days)						
0 (same day)	310 (45.7%)	2299 (41.5%)	2609 (41.9%)	--	--	--
1	118 (17.4%)	1075 (19.4%)	1193 (19.2%)	--	--	--
2	78 (11.5%)	546 (9.8%)	624 (10.0%)	--	--	--
3	37 (5.5%)	402 (7.2%)	439 (7.1%)	--	--	--

4	34 (5.0%)	312 (5.6%)	346 (5.6%)	--	--	--
5	37 (5.5%)	302 (5.4%)	339 (5.4%)	--	--	--
6	36 (5.3%)	301 (5.4%)	337 (5.4%)	--	--	--
7	28 (4.1%)	309 (5.6%)	337 (5.4%)	--	--	--

Table 2: Predictive variables for AKI on multivariable logistic regression analysis in patients undergoing surgery and radiological investigations with CM administration(n=6224)

	Odds ratio (95% CI)	***P* value**
Age at operation (years)	1.010 (1.004 – 1.017)	0.002
Male gender	1.336 (1.130 – 1.580)	0.001
SIMD deprivation	1.060 (0.998 – 1.127)	0.060
eGFR category (mL/min):		
<29 (reference)	--	
30-44	0.696 (0.505 – 0.960)	0.027
45-59	0.434 (0.319 – 0.592)	< 0.001
>60	0.230 (0.174 – 0.304)	< 0.001
Diabetes	1.103 (0.883 – 1.378)	0.387
ACE inhibitors or ARBs	1.252 (1.031 – 1.520)	0.023
NSAIDs	1.013 (0.824 – 1.246)	0.902
Statins	1.179 (0.968 – 1.435)	0.102
Loop diuretics	1.006 (0.804 – 1.259)	0.955
No. of prescribed drugs:		
None (reference)	--	
1-5	0.947 (0.567 – 1.581)	0.834
6-10	1.352 (0.813 – 2.248)	0.246
11-15	1.175 (0.693 – 1.993)	0.550
16-20	1.286 (0.737 – 2.244)	0.376
>20	1.123 (0.631 – 2.001)	0.693
Timing of CM exposure	0.972 (0.935 – 1.010)	0.146

Table 3. Ordinal logistic regression analysis by stage in patients with post-operative AKI undergoing surgery and radiological investigations with CM administration (n = 678).

	Odds ratio (95% CI)	***P* value**
Age at operation (years)	0.996 (0.982 – 1.010)	0.573
Male gender	1.137 (0.764 – 1.690)	0.526
SIMD deprivation	1.010 (0.879 – 1.161)	0.887
eGFR category (mL/min):		
<29 (reference)	--	
30-44	1.723 (0.746 – 3.984)	0.203
45-59	2.322 (1.040 – 5.186)	0.040
>60	3.270 (1.599 – 6.688)	0.001
Diabetes	1.294 (0.787 – 2.127)	0.310
ACE inhibitors or ARBs	1.252 (0.801 – 1.956)	0.323
NSAIDs	1.277 (0.796 – 2.048)	0.310
Statins	1.194 (0.769 – 1.854)	0.430
Loop diuretics	0.803 (0.480 – 1.342)	0.402
No. of prescribed drugs:		
None (reference)	--	
1-5	0.862 (0.279 – 2.669)	0.797
6-10	0.790 (0.257 – 2.434)	0.682
11-15	0.754 (0.232 – 2.449)	0.638
16-20	0.787 (0.226 – 2.738)	0.706
>20	0.653 (0.175 – 2.435)	0.525
Timing of CM exposure (days)	0.907 (0.823 – 1.000)	0.051