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ORIGINAL ARTICLE

Contrast-induced nephropathy following CT scan for trauma is not rare and is associated with increased mortality in South African trauma patients

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Abstract

Purpose Acute trauma patients are at risk for the development of acute kidney injury (AKI). One potential nephrotoxic agent, which a trauma patient may be exposed to, is iodinated contrast media (ICM). We aim to review the incidence and outcome of contrast-induced nephropathy (CIN) in trauma patients in a busy trauma service, and to identify potentially modifiable risk factors.

Methods During the period from December 2012 to April 2017, all patients who underwent a contrast-enhanced CT scan for trauma were included. Data were examined and outcome data were reviewed.

Results A total of 1566 patients required a CT scan following blunt trauma at our institution. Of this total 755 patients underwent a contrast-enhanced CT scan. There were 173 females (22.9%) and 582 males (77.1%). All these patients received intravenous contrast. A total of 143 (18.9%) were admitted to ICU, and 58 (7.7%) of patients died. Detailed electrolyte studies pre- and post-procedure were available for 312 patients. Of these 312 patients, 46 developed CIN (14.7%).There was no difference in the incidence of pre-CT AKI or deranged electrolytes between the patients who developed CIN and those who did not. The development of CIN was associated with an increased risk of death as well as increased need for renal replacement therapy as well as increased need for ICU.

Conclusion Contrast-induced nephropathy is a real risk in trauma patients undergoing contrast-enhanced CT scan for blunt trauma in our environment. Further work is needed to define and delineate risk factors.

Keywords Intravenous contrast · Acute kidney injury · Blunt trauma · Risk factors

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Introduction

Acute trauma patients are at risk for the development of acute kidney injury (AKI), and a multiplicity of potential aggravating etiological factors are present in these patients. These include haemorrhage, shock, sepsis and the administration of nephrotoxic agents. One potential nephrotoxic agent, which a trauma patient may be exposed to, is iodinated contrast media (ICM). ICM is most commonly administrated intravenously during CT scan and the most important adverse effects of ICM are hypersensitivity reactions, and contrast-induced nephropathy (CIN) [1–3]. CIN is defined as an acute renal insufficiency in patients with normal renal function or in patients previously diagnosed with chronic renal insufficiency preceding the diagnostic procedure involving contrast administration. According to the European Society of Urogenital Radiology (ESUR), significant worsening of renal function is determined on the basis of laboratory standards including creatinine clearance reduced by 25% or serum creatinine levels increased by 25% or 0.5 mg/dl (44.2 µmol/l) compared to the values before the procedure (within 3 days after contrast administration) [3]. The true incidence of this condition and even its existence as a real clinical entity is disputed. Most reports on CIN come from high-income countries (HIC) and include heterogeneous groups of patients receiving intra-vascular ICM for a variety of conditions emergent and elective, as well as diagnostic and therapeutic [4–7]. South Africa has an excessive burden of trauma and is a low middle-income country (LMIC) and hence has unique challenges, which make it difficult to extrapolate findings from HICs directly [8, 9]. In light of this, we set out to review the incidence and outcome of CIN in trauma patients in our busy trauma service in South Africa. We hoped to document the actual incidence of the condition in a relatively homogenous cohort of trauma patients and to identify potentially modifiable risk factors to predict the development of this condition.

Clinical setting

The city of Pietermaritzburg is the capital of KwaZulu-Natal (KZN) province and the largest city in the western half of KZN with one million inhabitants. The city is the referral point for Western KwaZulu-Natal, which is a predominantly rural area with a population of two million people. The burden of trauma is significant and is almost an even split between blunt trauma and penetrating trauma. The Pietermaritzburg Metropolitan Trauma Service (PMTS) provides and supervises trauma care across the city. There are a significant number of referrals from the rural districts of the western part of the province and the service admits over 2000 trauma patients a year.

Management algorithms

All blunt trauma patients are managed according to ATLS principles and resuscitated by the attending trauma staff on arrival in the emergency department. Patients who do not respond undergo a FAST scan and are then expedited to the operating room if there is free intra-abdominal fluid. All other patients are then selected for a CT scan based on the mechanism of injury and clinical findings. All patients who undergo CT scan are discussed with the attending trauma surgeon and undergo fluid resuscitation prior to being sent for CT scan. Fluid resuscitation is deemed adequate if there is documented urine output and a stable systolic blood pressure. A pre-CT scan workup includes blood urea and electrolytes in all patients. We are reticent to scan patients who we suspect have impaired renal function and carefully weigh up the risk–benefit ratio in these patients.

CT protocol

The CT scan protocol did not change during the period of the study. Three types of contrast material were used depending on availability: Omnipaque 300 (Iohexol), Iopamiron (Iopamidol) and Ultravist (Iopromide). For contrast-enhanced torso CT scans 100 ml of contrast was injected intravenously by an injector pump, the flow rate was set at 3 ml/s. For peripheral, upper extremities and carotid angiograms, 100–150 ml of Omnipaque 350, Ultravist 350 or Iopamiron 370 diluted into 50 ml of normal saline and infused by the injector pump at flow rate 5 ml/s.

Methods

The PMTS maintains a prospective digital registry. Ethics approval to maintain the registry has been obtained from the Biomedical Research Ethics Committee (BCA221/13 BREC) of the University of Kwa Zulu-Natal and from the Research Unit of the Department of Health. This digital registry is unique and has been discussed in the literature [9, 10]. The clerking medical staff enter the data onto an electronic pre-prepared clerking sheet. This process is the clerking process for all new admissions, meaning that the clinical data are entered in real time. As the data are entered they are then directly incorporated into the registry. The completed pre-prepared clerking sheet is then printed and becomes the patient's clinical record. At operation and at discharge a similar process is followed. This system combines the functions of a medical registry and a medical record system. It also combines an electronic system with a paper-based system and has been called the Hybrid Electronic Medical Registry.

The trauma database was interrogated for the period from December 2012 to April 2017. All patients over the age of 18 years who underwent a CT scan for blunt trauma were included. Data were examined for completeness and patients with missing admission blood results were excluded from the analysis. Outcome data were reviewed. This included in-hospital mortality, need for ICU and length of stay. AKI was defined according to the latest kidney Disease Improving Global Outcomes (KDIGO) guidelines using the presentation creatinine. The baseline creatinine was calculated according to the MDRD equation (as per KDIGO), using the patient's race, sex and age. AKI, as described by the KIDGO group is diagnosed according to either urine output criteria, serum creatinine measurement, or the use of renal replacement therapy (RRT). Contrast-induced nephropathy (CIN) is defined by ADQI/KDIGO criteria as a deterioration or impairment of renal function and can be measured as either a 25% increase in serum creatinine (SCr) from baseline or a 0.5 mg/dl (44 µmol/l) increase in absolute serum creatinine, within 48–72 h following the intravascular injection of contrast [1–3] (https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf). The renal insufficiency should be acute and should usually occur within 48–72 h after the administration of contrast and all other potential etiological agents for renal deterioration should have been excluded.

Statistical analysis

Means and standard deviations are reported for normally distributed data; median and inter-quartile range for data not normally distributed. The χ^2 test and Fisher's exact test were used for categorical data, and independent samples *t* test, Kruskal–Wallis, or Mann–Whitney *U* test for continuous data where appropriate. All *p* values were reported to three decimal places and statistical significance was defined as a two-sided *p* value 0.05. All data analyses were performed using SPSS 24.0 for Mac (SPSS, Chicago, IL).

Results

During the period under review, a total of 1566 patients required a CT scan following blunt trauma at our institution. Of this total 755 patients underwent a contrast-enhanced CT scan. There were 173 females (22.9%) and 582 males (77.1%). The median age was 31 years, ISS was 17, HR 91, Shock Index (0.8), Systolic BP (123 MmHg). All these patients received intravenous contrast. A total of 143 (18.9%) were admitted to ICU, and 58 (7.7%) of patients died. Detailed electrolyte studies pre-and post-procedure were available for 312 patients. Of these 312 patients, 46 developed CIN (14,7%). A total of 811 patients underwent a non-contrast-enhanced CT scan. The demographics of the cohort which did not receive contrast and the cohort which did receive contrast are compared in Table 1. The patients who required a contrast CT scan had significantly worse physiology and more severe injuries than those who did not.

Table 2 summarizes the demographic profile and physiology of the cohort of patients who underwent a contrast-enhanced CT scan and goes on to compare those who developed CIN and those who did not. There was no difference between those who developed CIN and those who did not in terms of GCS, shock, ISS or RTS. Similarly, Table 3 compares the biochemistry of the entire cohort of patients who underwent a contrast-enhanced CT scan. There was no difference in the incidence of pre-CT AKI or deranged electrolytes between the patients who developed CIN and those who did not. The presence of pre-CT AKI, the need for RRT and the need for ICU were associated with an increased risk

Table 1 Variables of entire cohort (*n* = 1566)

	Total (*n* = 1566)	No IV contrast (*n* = 811)	IV contrast (*n* = 755)	*P* value
Age	30 (24–40)	29 (23–39)	31 (25–41)	0.005
ISS	13 (13–22)	9 (3–16)	17 (9–26)	< 0.001
Shock	71	13	59	< 0.001
Shock index	0.7 (0.6–0.9)	0.7 (0.5–0.8)	0.8 (0.6–1.0)	< 0.001
RTS	107.2 (98.6–116.9)	107.5 (99.4–116.9)	106.8 (97.3–117.4)	0.115
Pre-CT AKI	68	27	41	0.081
Admission GCS	15 (12–15)	15 (13–15)	15 (8–15)	< 0.001
Base excess	− 1.1 (− 4.0 − 1.35)	− 0.4 (− 2.9–1.8)	− 1.4 (− 4.5–0.9)	< 0.001
Hb	13.1 (11.25–14.5)	13.6 (12.1–14.8)	12.4 (10.5–14.1)	< 0.001
Lactate	2 (1.2–3.4)	1.7 (1.1–2.8)	2.13 (1.2–3.72)	< 0.001
Dialysis	5	2	3	0.596
ICU	178	35	143	< 0.001
Demised	74	16	58	< 0.001

Continuous data—median and IQR

Table 2 Demographics and presentation data of patients who received CT scan with IV contrast

	No CIN ($n=266$)	CIN ($n=46$)	P value
Male sex (n, %)	207 (77.8)	35 (76.1%)	0.795
Urban vs rural (n, %)			
Urban	194 (72.9)	30 (65.2)	
Rural	32 (12.0)	6 (13.0)	
Unknown	40 (15.0)	9 (19.6)	0.649
Temp. °C (median, IQR)	36.6 (36.0–37.0)	36.3 (35.8–36.7)	0.007
Admission GCS (median, IQR)	15 (9–15)	14 (7–15)	0.493
Shocked on presentation (n, %)	25 (9.4)	5 (10.9)	0.912
ISS (median, IQR)	19 (13–29)	18 (9–27)	0.132
RTS (median, IQR)	106.5 (96.4–117.5)	108.9 (101.1–121.9)	0.227
Pre-CT AKI (n, %)	21 (7.9)	4 (8.7)	0.859

Table 3 Biochemistry and haematology results of patient cohort

	No CIN ($n=266$)	CIN ($n=46$)	P value
Hb g/dl (median, IQR)	11.9 (9.9–13.5)	12.2 (8.5–13.4)	0.425
pH (median, IQR)	7.390 (7.320–7.430)	7.380 (7.330–7.430)	0.651
HCO_3^- mmol/l (median, IQR)	23.2 (20.2–25.5)	22.5 (19.7–26.8)	0.856
BE mmol/l (median, IQR)	−1.7 (−4.7–0.8)	−3.55 (−6.6–2.20)	0.670
Lactate mmol/l (median, IQR)	2.40 (1.40–4.01)	2.05 (1.15–4.55)	0.699
Pre-CT urea mmol/l (median, IQR)	4.6 (3.4–5.7)	4.7 (3.1–6.7)	0.428
Pre-CT Cr umol/l (pre-CT) (median, IQR)	83 (68–103)	70 (50–99)	0.014
Post-CT urea mmol/l (median, IQR)	3.9 (2.9–5.7)	7.1 (3.7–13.5)	<0.0001
Post-CT creatinine umol/l (median, IQR)	68 (54–80)	108 (80–184)	<0.001

Table 4 Outcomes of whole cohort

	Total cohort ($n=755$)	Survived ($n=697$)	Demised ($n=58$)	P value
Pre-CT AKI (n, %)	41 (5.4)	33 (4.7)	8 (13.8)	0.001
Admitted to ICU (n, %)	143 (18.9)	119 (17.1)	24 (41.4)	<0.001
Received RRT (n, 5%)	3 (0.4)	1 (0.1)	2 (3.4)	0.001

Table 5 Outcomes of CIN cohort

	Total cohort ($n=755$)	No CIN ($n=266$)	CIN ($n=46$)	P value
Received RRT (n, 5%)	3 (0.4)	0 (0.0)	3 (6.5)	0.003
Admitted to ICU (n, %)	143 (18.9)	78 (29.3)	20 (43.5)	0.033
Demised (n, %)	58 (7.7)	17 (6.4)	7 (15.2)	0.038

RRT renal replacement therapy

of death. This is summarized in Table 4. Patients with chest trauma were compared with those with abdominal trauma, to control for the possibility of raised intra-abdominal pressure exacerbating AKI. There was no association between either chest or abdominal trauma with the development of CIN (23/125 vs 23/187 $p=0.145$ Chest * CIN) and (18/139 vs 28/173 $p=0.541$ Abd * CIN).

The development of CIN was associated with an increased risk of death as well as increased need for renal replacement therapy as well as increased need for ICU and Table 5 summarizes these results. Multivariate regression analysis was performed on the entire cohort to identify risk factors for death. This is shown in Table 6. Shock, admission GCS and post-CT creatinine levels are significant risk factors for death. The need for IV contrast is a very significant predictor of death but has a wide 95% CI.

Table 6 Multivariable regression analysis: outcome of mortality

	Significance	OR	(95% CI)
Shock	0.017	4.904	1.322–18.180
Admission GCS	0.017	0.876	0.785–976
IV contrast	0.016	19.594	1.760–217.098
Post-CT creatinine	< 0.001	1.008	1.004–1.012

Discussion

Traditionally the administration of intra-vascular contrast was regarded as a risk factor for the development of post-CT scan AKI and was termed contrast-induced nephropathy (CIN) [1–3]. It has been described as the third leading cause of AKI and as it is iatrogenic, a great deal of emphasis has been placed on preventing it. It is seen in a wide range of patients who needed intravascular contrast as part of a radiological investigation. These include patients undergoing both diagnostic and interventional procedures and those receiving both intravenous and intra-arterial contrast. The traditional explanation of the pathophysiology is that renal blood flow is redirected, leading to tubular insult through an ischaemic mechanism. However, recently some authors have questioned whether the condition actually exists [1–6]. The American College of Radiology Manual has gone so far as to suggest changing from the term CIN to the more neutral term of post-contrast acute kidney injury. The causality of the administration of intravenous iodinated contrast material and post-procedural deterioration in renal function has been challenged [3]. Detractors point out serum creatinine levels may fluctuate for a number of reasons such as sex and body mass. In addition, including patients receiving intravenous contrast with those undergoing more invasive procedures, which involve intra-arterial administration of contrast results in a heterogeneous patient sample, which makes it difficult to draw conclusions about the true incidence and aetiology of the condition [1–6]. These are valid criticisms as there are many factors, which may contribute to the development of AKI in such cohorts of high-risk patients.

American authors have shown that the presence of diabetes and an ISS > 25 are associated with the development of CIN [1–4]. In our series, patients with an increased ISS were more likely to require a contrast-enhanced CT scan. This implies that these patients were at increased risk of developing AKI regardless of whether or not they were exposed to intravenous contrast and this makes it difficult to demonstrate a correlation between the administration of intravenous contrast and AKI. In our cohort, patients undergoing contrast-enhanced CT scan had significantly worse physiology and more severe injuries than those who underwent a non-contrast-enhanced CT scan. There were thus many factors which may have contributed to the development of AKI in these patients apart from the administration of intravenous contrast. It is thus difficult to ascribe direct causality to the administration of intravenous contrast in these patients and the aetiology of AKI following contrast-enhanced CT scan is almost certainly multi-factorial, in these patients.

Our study focuses on patients who underwent diagnostic CT scans all of whom received intravenous contrast. This is a relatively homogenous cohort of young trauma patients and this makes our findings interesting. The incidence of diabetes in our cohort of young trauma patients is relatively low in comparison to these reports from North America, which include patients requiring intravenous and intra-arterial contrast for a broad spectrum of pathologies. We had a high incidence of CIN of 14.7% and the mortality rate in this group of patients was twice that in the patients who did not develop post-procedure AKI. Previous work from our sister trauma unit in Durban, South Africa, also showed an association between contrast administration and the development of AKI [11].

Our incidence of CIN in trauma patients is higher than that reported from the USA which is in the order of 4% and this implicates local systematic factors in the aetiology of this condition [1–4]. Identifying risk factors for the development of CIN is therefore important as it may allow us to identify vulnerable patients and ultimately to intervene in their management. However, this study did not set out to investigate the causes and risk factors for the development of CIN, and therefore did not pre-specify potential variables which may have precipitated the development of CIN. Future work based on this database may try and identify these risk factors. Currently when the following variables: age, ISS, base excess, lactate, haemoglobin, pre-CT creatinine, systolic blood pressure and temperature are entered into an multi-variate analysis (MVRA) for CIN as the outcome, the only variables that remain are systolic blood pressure ($p = 0.022$, OR 1.023 95% CI 1.003–1.042) and temperature ($p = 0.037$, OR 0.629 95% CI 0.407–0.972). This represents significant collinearity as ISS is linked to both base excess, lactate, haemoglobin, systolic blood pressure and temperature.

Currently, we actively look for factors which suggest an at-risk patient and ensure that all such at-risk patients receive aggressive fluid resuscitation prior to undergoing contrast-enhanced CT scan. We repeat all bloods including BUN, serum creatinine as well as serum lactate prior to sending these high-risk patients to CT scan. We also have a dedicated post-CT scan protocol for these patients and we repeat all their bloods 12 h and 24 h post-CT scan. Despite this, we are unclear that asking for a formal blood urea and nitrate (BUN) and serum creatinine cannot be supported by this data as there was little difference in pre-CT scan BUN between the patients who developed CIN and those who did not. In Table 3, the median serum creatinine pre-CT scan is

statistically significantly lower [p0.014] (although clinically not a substantially significant difference) in the patients who developed CIN. This would suggest that serum creatinine is not a useful marker for the development of CIN and this may simply reflect the fact that serum creatinine has a time lag of 24–48 h as a marker of renal injury.

The development of CIN in our environment is ominous as it is associated with an increased risk of death as well as increased need for renal replacement therapy and ICU. Multivariate regression analysis identified shock, admission GCS and post-CT creatinine levels as significant risk factors for death. The need for IV contrast was also identified as a significant predictor of death but its wide 95% CI means the sample size is too small for the event rate of the outcome. To confirm or refute this finding, this study will need to be replicated in a larger cohort to see if the same hypotheses hold true.

There are a number of limitations to this study. South Africa despite its huge burden of trauma has a problem with its retrieval system for these patients. Long pre-hospital delays and inadequate assessment of these patients in the periphery probably contribute to this high incidence and lack of clarity as to how these patients were managed in the periphery is difficult to control for [8, 9]. We do not use NSAIDS in these patients, but they may well have received potentially nephrotoxic drugs in the periphery. Another confounding factor is the high incidence of rhabdomyolysis in our environment. Our group has published on this topic extensively. Rhabdomyolysis is a common problem in South Africa due to beating injuries with whips or sticks. Other common causes of rhabdomyolysis are limb compartment syndromes. Both of these syndromes are diagnosed clinically and by urine analysis, not via measurement of serum creatinine kinase (CK) in our unit and serum CK is not routinely measured in our unit. This protocol is based on previous work done by our group [11, 12]. CK does indeed cause problems with measuring serum creatinine, however many substances such as lipids, excess protein, albumin, bilirubin, cefoxitin and other antibiotics can also interfere with the assay for serum creatinine. We are unable to control for all of these potential confounding substances and this is another limitation of our study.

Conclusion

Contrast-induced nephropathy is a real risk in trauma patients undergoing contrast-enhanced CT scan for blunt trauma in our environment. In addition, the development of CIN is associated with increased mortality. Local systematic factors probably contribute significantly to this incidence and further work is needed to define and delineate these risk factors. Ultimately, we need to develop strategies to identify vulnerable patients and interventions to correct these risk factors.

Author contributions AAB: primary author, data analysis. VK: analysis and drafting. DS: manuscript editing and assistance with statistics. GL: design of data capture instrument. JB: database maintenance and data retrieval. PB: drafting, reference checking. DC: senior author, general supervision, co-ordination and assistance at all levels.

Compliance with ethical standards

Conflict of interest AAB, VK, DS, JB, GL, PB, DC declare no conflict of interest relevant to this manuscript.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Ethical approval We have ethics approval to keep and use this database (BE 207/09, 221/13).

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