Contrast-Induced Nephropathy among Israeli Hospitalized Patients: Incidence, Risk Factors, Length of Stay and Mortality

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ABSTRACT: **Background:** Radiological procedures utilizing intravascular contrast media are being widely applied for both diagnostic and therapeutic purposes. This has resulted in the increasing incidence of procedure-related contrast-induced nephropathy. In Israel, data on the incidence of CIN and its consequences are lacking.

Objectives: To describe the epidemiology of CIN among hospitalized patients in the Western Galilee Hospital, Nahariya (northern Israel), and to explore the impact of CIN on mortality and length of stay.

Methods: The study group was a historical cohort of 1111 patients hospitalized during the year 2006 who underwent contrast procedure and whose serum creatinine level was measured before and after the procedure. Data were electronically extracted from different computerized medical databases and merged into a uniform platform using visual basic application.

Results: The occurrence of CIN among hospitalized patients was 4.6%. Different CIN rates were noticed among various high risk subgroups such as patients with renal insufficiency and diabetes mellitus (14.1%–44%). Average in-hospital length of stay was almost twice as long among patients with CIN compared to subjects without this condition. Furthermore, the in-hospital death rate among CIN patients was 10 times higher. A direct association was observed between severity of CIN based on the RIFLE classification and risk of mortality.

Conclusions: Low CIN occurrence was demonstrated in general hospitalized patients (4.6%), and high rates (44%) in selected high risk subgroups of patients (with renal insufficiency or diabetes mellitus). Furthermore, prolonged length of stay and high in-hospital mortality were directly related to CIN severity.

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KEY WORDS: contrast-induced nephropathy, hospitalized patients, incidence rate, Israel, length of stay, mortality

Even in light of modern and less harmful contrast media solutions, their increased use during standard and new radiological procedures has resulted in the growing incidence of contrast-induced nephropathy, an iatrogenic disorder caused by exposure to contrast media [1].

CIN is a complex syndrome of acute kidney injury occurring after the administration of contrast media. The definition includes absolute or relative increase in serum creatinine level following exposure to contrast media compared with baseline value. Usually the rise in SCr occurs within 24–48 hours of the exposure, with creatinine level typically peaking 3–5 days after the procedure and returning to baseline or near baseline value in 1–3 weeks [2]. The cutoff increase in creatinine defining CIN differs in various studies (from 20 to 50%, or in absolute values from 0.5 to 1 mg/dl), making it difficult to compare the results. The most common definition currently used is a > 25% relative increase or an absolute increase of ≥ 0.5 mg/dl in SCr from baseline value 48–72 hours after exposure to contrast media [1]. On the basis of this definition, CIN is the third leading cause of hospital-acquired acute kidney injury, accounting for 10% of all cases [3] and associated with poor outcome including high in-hospital mortality rates [4]. An overall incidence of CIN in the general hospitalized population is reported to be 0.6–2.3% [5]. However, in several patient subgroups, such as patients with renal insufficiency and diabetes mellitus, the prevalence of CIN is significantly higher [4,6]. To the best of our knowledge, no study addressing the epidemiology of CIN has been conducted in Israel. The present study was undertaken to determine the incidence and outcome of CIN in a heterogeneous population in a public governmental hospital in the north of Israel.

PATIENTS AND METHODS

We conducted a retrospective cohort study among patients hospitalized at the Western Galilee Hospital in Nahariya,

CIN = contrast-induced nephropathy

SCr = serum creatinine

a town in northern Israel. The study group comprised all adults and adolescents (aged 16 and above) admitted in 2006 (1 January to 31 December) who underwent at least one procedure with contrast media. Data analysis refers only to the first procedure. Exclusion criteria were: a) age < 17 years, b) pregnant women treated at the High Risk Pregnancy Unit/delivery room, c) patients with end-stage renal disease undergoing chronic dialysis who were hospitalized during the study period and/or patients with pre-procedure Scr ≥ 6 mg/dl. Patients who underwent dialysis therapy because of acute kidney injury were not excluded from the data analysis.

Data analysis was performed for the following procedures: X-ray with contrast media, computed tomography, CT-angiography and intravenous pyelogram. Coronary procedures were excluded because of missing computerized data on the date of the procedure.

DATA COLLECTION

Selective data were electronically extracted from the following hospital computerized medical databases:

- discharge summary records – for data on dates of patient's admission and discharge, patient's ID and hospital admission number, patient's birth date, gender and status at discharge (alive or dead).
- diagnoses records – for date of discharge for each patient diagnosed with at least one of the following medical conditions (ICD-9 coded): Chronic Kidney Disease, Heart Failure, Diabetes Mellitus, Hypertension, Sepsis, Ischemic Heart Disease, and Cancer.
- procedure records – for data on dates of patient's exposure to contrast media such as CT, X-ray with contrast media, CTA and IVP.
- laboratory records – for patient's SCr level.

In order to merge all the above mentioned data into a uniform platform and enabling the creation of the necessary new variables needed for data analysis, new computerized programs were written using visual basic application.

DEFINITION OF CIN

CIN was defined as an increase in SCr level, compared to basal value, of at least 0.5 mg/dl during 1–5 days after exposure to contrast media. Basal SCr level was defined as the last level available prior to contrast exposure. Normal baseline renal function was defined as SCr < 1.2 mg/dl.

DATA ANALYSIS

Data analysis was carried out using SPSS (version 11.5) software (SPSS Inc., Chicago, IL, USA). Dichotomous variables – such as gender, presence of CIN (yes/no), presence of comorbidity: chronic kidney disease, heart failure, diabetes mellitus, hypertension, sepsis, ischemic heart disease and cancer (yes/no), exposed to contrast media (yes/no) – were described as frequencies. Means and standard deviations (SD) were calculated for continuous variables (age, length of stay and SCr). Incidence rates of CIN were calculated for the total population and for selected subgroups. The demographic (age and gender) and clinical (comorbidity) characteristics of subjects developing CIN were compared to attributes of patients who did not develop CIN, using chi-square tests (for dichotomous variables), and *t*-tests (for continuous variables). Comparison of outcome variables was also carried out between the two groups, using measures such as length of stay and mortality. The association between CIN and mortality was tested using logistic regression models. The association between the clinical consequences of CIN and severity of renal impairment was tested using the RIFLE classification (risk, injury, failure) based upon data of SCr levels [7]

RESULTS

Data on SCr level were available for 2187 (98.2%) of the 2227 admissions of patients exposed to procedures using contrast media. About half of these admissions, 1111 (50.8%), were subjects with at least two SCr measurements, one taken before and the other 1–5 days after exposure. Demographic and clinical characteristics of patients with at least one known SCr level and of patients with pre- and postprocedure SCr level are presented in Table 1.

Patients' age ranged from 17 to 98 years, average 59.3 (SD 19.00). Females were significantly older than males ($P < 0.001$). Data analysis showed that CIN occurred among 4.6% of 1111 hospital admissions exposed to contrast media. In patients with normal baseline renal function (SCr < 1.2 mg/dl), even in the presence of diabetes, the incidence rate of CIN was low (less then 3%). However, higher rates were observed among selected subgroups: the cumulative incidence of CIN among patients with renal insufficiency (basal SCr level ≥ 1.2 mg/dl or 1.3 mg/dl) was 14.1% and 21.1% respectively. The highest CIN incidence (44.0%) was demonstrated in patients who had diabetes in addition to renal insufficiency (basal SCr level ≥1.3 mg/dl) [Table 2].

The average age of CIN patients (64.4 years, SD 17.6) was higher than that of patients who did not develop CIN (59.0 years, SD 19.0, $P = 0.04$).

CIN was more prevalent among patients who had comorbidities, such as sepsis, chronic kidney disease, heart failure, cancer, ischemic heart disease, diabetes, and hypertension. Yet, only the presence of sepsis and chronic kidney disease were statistically significantly associated with CIN [Table 3].

The average length of stay among patients with CIN was almost twice as long as among patients without CIN [24 days

CTA = computed tomography-angiography
IVP = intravenous pyelogram

Table 1. Demographic and clinical characteristics of study populations

	Known pre-exposure SCr level (N=2,187)		Known pre & post-exposure SCr level* (N=1,111)	
	N	%	N	%
Gender				
Male	1073	49.1	550	49.5
Female	1114	50.9	561	50.5
Total	2187	100.0	1111	100.0
Age (yrs)				
17-24	189	8.6	68	6.1
25-44	443	20.3	171	15.4
45-64	707	32.3	354	31.9
65-74	398	18.2	231	20.8
75+	450	20.6	287	25.8
Total	2187	100.0	1,111	100.0
Age (yrs), mean ± SD				
Male	53.9 ± 19.46		56.6 ± 19.47	
Female	57.6 ± 19.37		62.0 ± 18.11	
Total	55.8 ±19.50		59.3 ± 18.98	
Comorbidity				
HTN	258	11.8	150	13.5
IHD	116	5.3	66	5.9
DM	150	6.9	95	8.6
CKD	28	1.3	25	2.3
Cancer	268	12.3	165	14.9
HF	49	2.2	40	3.6
Sepsis	32	1.5	27	2.4

* Post exposure = 1–5 days after exposure to contrast media

HTN = hypertension, IHD = ischemic heart disease, DM = diabetes mellitus, CHD = chronic kidney disease, HF = heart failure

Table 2. Incidence of CIN (%) by presence of diabetes mellitus and renal insufficiency

Risk group	N	No. of CIN (%)	Relative risk
Total population	1111	51 (4.6)	
No DM, No RI	878	27 (3.1)	1
DM, No RI	77	2 (2.6)	0.83
RI*, No DM	156	22 (14.1)	4.5
RI**, No DM	90	19 (21.1)	6.8
DM & RI*	18	5 (27.7)	8.9
DM & RI**	9	4 (44.4)	14.3

* Basal SCr ≥ 1.2 mg/dl

** Basal SCr ≥ 1.3 mg/dl

DM = diabetes mellitus, RI = renal insufficiency

(SD 21.73) vs. 13 days (SD 12.55) respectively, $P < 0.001$]. Mortality rates among the former were ten times higher (31.4% vs. 3% respectively, $P < 0.001$). Using a logistic regression model as control for potential confounders – characteristics that were significantly associated with mortality in the univariate analysis (age, chronic kidney disease, sepsis) – also revealed a 10 times higher risk of mortality (odds ratio = 9.8, 95% confidence interval 4.4–22.0) among patients who developed CIN as compared to those who did not.

Higher odds ratios for in-hospital mortality (after controlling for confounders) were also noticed with increasing severity of CIN (RIFLE classification) [Table 4].

DISCUSSION

To the best of our knowledge this is the first study on the epidemiology of CIN in a retrospective cohort of hospitalized patients in a public governmental hospital in Israel. This study follows our recent publication describing the incidence and outcome of acute kidney injury in Israel [8]. In line with previous studies [9-12], low rates of CIN (4.6%) were demonstrated in the total study population, even in the presence of diabetes mellitus. However, when subgroup analysis was conducted among selected "risk groups" (such as patients with renal insufficiency), higher rates (14.1–21.1%) were demonstrated.

The pathogenesis of CIN is not clearly understood. Thus far, several pathophysiological mechanisms of CIN have been proposed, including direct toxicity to renal tubular epithelium, presence of oxidative stress, ischemic injury, and tubular obstruction [13]. Risk factors for CIN development have been thoroughly examined [1,3,4,6,14-16] and, as noted in our study, preexisting renal impairment, diabetes mellitus and advanced age were found to be important contributors for CIN development. The reasons for the higher risk of developing CIN in the elderly have not been carefully studied, but this entity is most probably multifactorial in nature, including factors such as age-related changes in renal function (diminished glomerular filtration rate and decreased tubular secretion and concentration ability) [12,17,18]. Impaired renal function is the major risk factor for CIN [19] because it is associated with decreased vasodilator response and with a slower clearance of contrast media [20]. Although rates of CIN in diabetic patients with preserved renal function were low (2.6%), we found that a combination of diabetes mellitus and renal insufficiency has a synergistic (more than multiplicative) effect on CIN occurrence. CIN occurred in 2.6–21.1% of patients with one risk factor (diabetes/Scr 1.2–1.3 mg/dl/ Scr ≥ 1.3 mg/dl) and in 27.7–44.4% of the patients with diabetes and renal insufficiency combined. In contrast to our expectation, CIN rates among patients with diabetes mellitus were lower than that among patients without the disease. We

assume that the small sample size of patients with diabetes and normal SCr (N=77) may result in an unstable CIN rate, as demonstrated in this group [Table 2]. Furthermore, the high proportion of patients with diabetes without SCr measurement after exposure to contrast media (36.6%) might result in a selection bias, manifested by underestimation of CIN incidence in this group of patients.

Our finding of a higher in-hospital death rate among CIN patients is consistent with previous studies [4,6,14,15,21-24]. The causal nature of this relationship is not clear, and because of the potentially confounded nature of these relationships (higher mortality and longer length of stay due to patients' severe sickness) it is unknown what proportion of mortality or morbidity would be avoided by CIN prevention. However, in the logistic models that included other variables that were related to mortality, CIN was still a significant predictor of death.

LIMITATIONS

Several methodological limitations should be mentioned. First, coronary procedures were excluded from the data analysis because of missing computerized data specifying the procedure date. Therefore, our CIN rates refer only to the following procedures: X-ray with contrast media, CT, CTA and IVP, and might therefore represent an underestimate of CIN incidence. Second, SCr data before and after exposure to contrast media were available for only 49.9% (1111) of the total number of hospitalized patients who underwent at least one contrast media procedure. Relying upon this selective group, probably characterized by the presence of more risk factors for CIN (compared to patients with missing data), might have introduced some selection bias, manifested by overestimation of CIN incidence. However, since exposure to contrast media is a known risk factor for acute kidney disease, absence of SCr results among some of these patients does not mean they represent a selective population with minimal or no chance of developing acute kidney disease. Third, discharge summary records – the source for examining the relationship between acute kidney disease and other patients' comorbidities – had no data on temporal relationship. Data analysis was therefore treated as cross-sectional, with prevalence ratios and odds ratios calculated. Fourth, some of the patients, especially those with SCr > 1.2 mg/dl, might have received prophylactic measures like hydration and N-acetylcysteine. Since there is no ICD-9 code for pharmacological therapy, data regarding prophylactic measures were not available and therefore we did not estimate the possible effect of prophylactic measures on CIN incidence. Fifth, the study was conducted in a single general hospital in northern Israel. Although internally valid, it does not necessarily ensure external validity to all Israeli hospitalizations.

Table 3. Prevalence ratios and odds ratios for contrast-induced nephropathy by selected medical conditions (N=1,111)

Disease		Total (N=1,111)		Acute kidney disease (N=51)					
		N	%	N	%	PR	OR	95% CI	*P* value
Sepsis	Yes	27	100.0	8	29.6	7.4	10.2	4.2-24.6	‹0.001
	No	1084	100.0	43	4.0				
CKD	Yes	25	100.0	8	32.0	8.0	11.4	4.6-27.9	‹0.001
	No	1086	100.0	43	4.0				
HF	Yes	40	100.0	4	10.0	2.3	2.4	0.8-7.0	0.09
	No	1071	100.0	47	4.4				
DM	Yes	95	100.0	7	7.4	1.7	1.8	0.8-4.0	0.17
	No	1016	100.0	44	4.3				
IHD	Yes	66	100.0	5	7.6	1.7	1.8	0.7-4.6	0.23
	No	1045	100.0	46	4.4				
HTN	Yes	150	100.0	10	6.7	1.6	1.6	0.8-3.2	0.19
	No	961	100.0	41	4.3				
Cancer	Yes	165	100.0	10	6.1	1.4	1.4	0.7-2.9	0.32
	No	946	100.0	41	4.3				

PR = prevalence ratio, OR = odds ratio, CI = confidence interval

Table 4. Logistic regression model to predict in-hospital mortality by RIFLE classification (N=1111)

RIFLE*	% deceased	OR**	95% CI	*P*
No CIN***	3.3	1.0		
Risk	20.7	3.9	(1.2, 12.0)	0.01
Injury	29.4	8.6	(2.3, 32.0)	0.001
Failure	33.3	11.6	(1.5, 89.7)	0.01

* RIFLE [7]

** Adjusted for chronic kidney disease, sepsis and age.

*** Contrast-induced nephropathy

CONCLUSIONS

The study included a heterogeneous population, admitted throughout the year to various hospital wards in which they underwent various procedures. Although rare in the general hospitalized population (4.6%), CIN occurs frequently in patients with underlying renal dysfunction, and in the elderly. Furthermore, the presence of two risk factors for CIN (diabetes and renal insufficiency) has a synergistic (more than multiplicative) effect on CIN occurrence. The high proportion of patients without SCr measurement emphasizes the necessity to enhance knowledge and physicians' awareness to the importance of renal function monitoring following exposure to contrast media. It is necessary to continue collecting and analyzing similar future data in order to both identify

trends in CIN incidence and outcomes (mortality, length of stay) and to assess the impact of relevant interventions such as N-acetylcysteine. Moreover, the significant association between CIN and increased mortality emphasizes the importance of early detection and efforts devoted to reducing the incidence of CIN – a valuable clinical and research goal.

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