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The role of osmolality in the incidence of contrast-induced nephropathy: A systematic review of angiographic contrast media in high risk patients

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The role of osmolality in the incidence of contrast induced nephropathy: A systematic review of angiographic contrast media in high risk patients.

Background. The role of osmolality of contrast media (CM) in the pathogenesis of contrast-induced nephropathy (CIN) has been suggested by studies comparing high osmolality CM (>1500 mOsm/kg) with low-osmolality CM (550–850 mOsm/kg), and by the results of a recent comparison of a CM isotonic to plasma (iodixanol, 290 mOsm/kg) with a low-osmolality CM (iohexol, 844 mOsm/kg) in high-risk patients undergoing cardiac or peripheral angiography.

Methods. Using prospectively defined search criteria, we performed a systematic overview of prospective, randomized, controlled studies of CIN in renally impaired patients receiving intra-arterial doses of iodixanol or low-osmolality, nonionic CM, and conducted a systematic review of the data from those studies to determine whether the osmolality of CM was predictive of CIN incidence.

Results. Seventeen primary studies met the selection criteria, for a total of 1365 patients. Overall, the incidence of CIN was 16.8%. A multivariate logistic regression model showed that the risk of CIN is similar with the iso-osmolality iodixanol and the low-osmolality iopamidol (796 mOsm/kg). The risk of CIN was significantly lower with iodixanol and iopamidol compared to iohexol. The incidence of CIN with iohexol was also significantly higher than with iopamidol, despite their similar osmolalities.

Conclusion. These data suggest that factors other than osmolality play a significant role in the pathogenesis of CIN, at least for agents with osmolalities of 800 mOsm/kg or less.

Contrast-induced nephropathy (CIN) is an acute decline in renal function after administration of an iodinated contrast agent in the absence of an alternative cause [1, 2]. Development of CIN is defined by a transient increase in concentration of serum creatinine (SCr) relative to baseline levels. The definition of the point at which a patient develops CIN varies from clinical study to clinical study. Definitions range from absolute (0.5 to 1.0 mg/dL) to relative (10%, 25%, 50%, or 100%) increases over baseline levels. In the vast majority of clinical trials, however, CIN has been defined as a relative rise in SCr ≥25%, or as an absolute increase ≥0.5 mg/dL from baseline [3, 4]. Based on this definition, the overall incidence of CIN is estimated to be 0.6% to 2.3% [5]. In patients with cardiovascular pathology undergoing angiography procedures, the incidence of CIN is higher, and ranges from 3.3% to 14.5% [6, 7]. Chronic kidney disease, defined as SCr stably ≥1.5 mg/dL, or a calculated or estimated creatinine clearance (CrCl) <60 mL/min, is the most important factor for the development of CIN [1, 2, 6]. In the vast majority of cases, a rise in SCr occurs within 24 to 48 hours of exposure to iodinated contrast media (CM), with a return to baseline or near baseline within 7 to 10 days [4, 8]. Dialysis as a result of CIN is required in 0.3% to 0.7% of patients undergoing angiography [6, 7]. Almost every patient who develops acute renal failure requiring dialysis shows a significant SCr rise already at 24 hours after the exposure to iodinated contrast [9]. Patients who develop contrast-induced acute renal failure are at significantly higher risk of death, both in hospital and at 1 year [6, 10–12]. The prognosis is particularly unfavorable in patients with preexisting renal compromise [10, 11].

Contrast agents cause nephrotoxicity through direct toxicity to tubular cells and renal medullary ischemia. Previous meta-analyses of CM found that the use of nonionic, low-osmolality versus ionic, high-osmolality contrast agents diminished the risk of CIN in high-risk patients [13–15]. This led to the generally accepted concept that osmolality contributed to the nephrotoxicity of CM, so-called "osmotoxicity." Recently, a prospective, double-blind, randomized, multicenter trial (the NEPHRIC study) provided further support for this concept. The study patients had mild-to-moderate renal failure (mean baseline SCr 1.5–1.6 mg/dL), diabetes, and underwent cardiac or peripheral angiography. The

Key words: contrast-induced nephropathy, osmolality, nonionic contrast media, acute renal failure.

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Table 1. Chemical structure and physicochemical properties of iodine-based contrast agents

Ionicity	Chemical structure	Osmotic class	Representative compounds	Osmolality (mOsm/kg)	Viscosity (cPs at 20°C)	Viscosity (cPs at 37°C)
Ionic	Monomer	High osmolality	Diatrizoate, Meglumine (Renografin, Conray, Hypaque)	1400–1800	6	4
	Dimer	Low osmolality	Ioxaglate (Hexabrix)	600	15	8
Nonionic	Monomer	Low osmolality	Iohexol (Omnipaque), Iopamidol (Isovue) Ioversol (Optiray) Iopromide (Ultravist)	600–850	9–21	5–10
	Dimer	Iso-osmolality	Iodixanol (Visipque)	280	27	12

incidence of CIN was significantly lower with the iso-osmolality agent iodixanol (290 mOsm/kg) compared to the low-osmolality agent iohexol (844 mOsm/kg) [16]. Based on the results of this study, it has been suggested that an iso-osmolality agent would be less likely to cause renal injury to patients with preexisting renal impairment compared to all low-osmolality CM. However, CM media differ in a number of other physicochemical characteristics, including ionicity, viscosity, and molecular size (monomer vs. dimer) (Table 1).

Several other studies have evaluated the nephrotoxicity of iso- and low-osmolality nonionic CM in patients with preexisting renal failure, although these studies were not designed as head-to-head comparison trials. Therefore, we performed a systematic overview of all prospective studies of CIN in patients undergoing cardiac or peripheral angiography, and analyzed the pooled data from studies in patients with baseline renal insufficiency to determine whether the available data support the osmotoxicity concept. Specifically, we asked whether iso-osmolality CM are associated with less nephrotoxicity compared to all low-osmolality CM.

METHODS

We used the following strategies to identify the primary studies to be included in the analysis: an electronic search of medical databases and a review of the reference lists from review articles that fulfilled our eligibility criteria.

Identification of systematic reviews

A total of 81 reviews on CIN following intravascular administration of iodinated CM were retrieved using an online search on MEDLINE and the following key words: "contrast media," "nephrotoxicity," "review." Seven of these were selected for further assessment of cited references.

Study identification

A systematic and comprehensive online search was performed for publications printed from January 1991 to September 2004. A librarian undertook an iterative process, for each database, to refine the search strategy through testing of several search terms and incorporation of new search terms as new relevant citations were identified. The search included the following databases: EMBASE, MEDLINE, Biosis Previews, Derwent Drug File, Pascal, SciScearch Cited Ref Sci.

A combination of the following key words was used: "contrast/imaging medium/a," "contrast/imaging agent," as well as individual nonionic contrast media nonproprietary/proprietary names, "complications/reactions/effects," "contrast-induced nephropathy," "nephropathy," "nephrotoxicity," "chronic renal failure," "chronic renal insufficiency," "renal/kidney impairment," "creatinine," "controlled clinical study." A total of 1594 citations were identified.

Selection of primary studies

The following criteria were prospectively defined to select studies for inclusion in the review: (*1*) English language; (*2*) publication in peer-reviewed journals; (*3*) either randomized, double-blind comparisons of iodinated contrast media, or prospective, randomized studies of the safety and efficacy of measures to prevent CIN (hemofiltration, N-acetylcysteine, or other drugs); (*4*) the exact number of patients who had received a specific nonionic contrast agent (e.g., iodixanol, iohexol, iopamidol, etc.) clearly reported; (*5*) the exact number of patients who had received or not received any preventive measure other than hydration clearly reported; (*6*) adequate hydration before and after the procedure; (*7*) study populations with mean baseline SCr levels between 1.5 and 3.5 mg/dL and/or mean baseline CrCl between 20 and 60 mL/min; (*8*) intra-arterial CM administration; (*9*) definition of CIN end point as an absolute increase $\geq$0.5 mg/dL or a relative increase $\geq$25% in SCr over baseline at 1 to 7 days after the CM administration.

Due to the limited precision of the index terms used by the online databases, an initial screening was performed by one qualified reviewer to discard citations that were clearly not pertinent (animal/in vitro studies, studies not related to contrast media, contrast media used for glomerular filtration rate measurement, contrast media pharmacokinetics, congress abstracts/posters). This preliminary screening process yielded 145 potentially relevant citations. Subsequently, two qualified reviewers independently screened the titles and abstracts of each of these, and if either reviewer believed that a citation could be relevant, the full-text article was retrieved and

the selection criteria were applied. At this step, citations were excluded for the following reasons: editorials, letters, reviews, re-published studies, administration route different than intra-arterial. The full text of the remaining 62 citations was retrieved for full review.

We masked the results (i.e., obscured them with a black marker from the tables and text) of all publications selected for full review. Two individuals independently evaluated each masked article to determine eligibility. All disagreements were resolved by consensus. The consensus process required individuals to discuss the reasoning for their decisions. If one individual realized that she or he had made an error, then the process was repeated. Consensus was obtained in all cases, and therefore an independent third adjudicator was never required to resolve disagreements.

Following the identification of the previously published reviews and the selection of the primary studies, the reference section of both the systematic reviews and the primary studies was reviewed to search for additional primary studies that could have been missed by the electronic search. No additional relevant publications were identified.

Patient selection

We evaluated only data from patients who had received a nonionic contrast agent to avoid any potential contribution of ionicity to nephrotoxicity. In case prospective, randomized studies of the safety and preventive efficacy of hemofiltration, N-acetylcysteine, or other drugs were selected, we reviewed only the data from the placebo or control arm of those studies to eliminate the confounding effect of the preventative strategy.

Analysis

The data from the selected studies were pooled together overall and by the contrast agent used. For continuous variables, the mean was calculated using the means of each individual study weighted by the number of patients in that study. The standard deviation for the pooled data was calculated using standard deviation from each study with an assumption that all the studies had approximately the same level of variability. When only mean values were reported, a graphic display of standard deviation versus mean was employed to interpolate the values for the unknown standard deviation.

Baseline patient characteristics (i.e., age, gender, diabetes mellitus, CM dose, and baseline SCr) in CM groups (iohexol, iodixanol, and iopamidol) were compared by pairwise *t* tests (iodixanol vs. iohexol, iopamidol vs. iohexol, etc.) for continuous variables and a chi-square test for categorical variables. Neither homogeneity testing nor comparisons of CIN incidence were performed for iopromide, iomeprol, ioxilan, and iopentol study groups versus other study groups because the sample size of the studies with these agents was too small.

The outcome chosen for analysis was the incidence of CIN, defined in each study as a relative rise in SCr $\geq$25%, or as an absolute increase $\geq$0.5 mg/dL from baseline. To obtain the incidence rate of CIN, we pooled the CIN cases in the different primary studies and then divided the number of CIN cases by the overall number of the selected patients in the same studies.

The risk of CIN in CM was compared by a multivariate logistic regression model, and odds ratios (OR) and 95% CIs were used to quantify the likelihood of having CIN. This multivariate model was developed using SAS software version 8.2 (Cary, NC, USA). The study-level patient baseline characteristics, including age, gender, percentage of patients with diabetes mellitus, volume of CM administered, and baseline SCr, were treated as covariates. Goodness-of-fit of the logistic model was tested using the Hosmer and Lemeshow test. For CM comparison, the largest patient group (iohexol) was treated as the reference group.

RESULTS

Selected studies

A schematic representation of the process used to select the studies included in this meta-analysis (primary studies) is shown in Figure 1. Overall, this strategy identified 17 primary studies [13, 14, 16–30]. Thirteen of these studies were placebo-controlled, randomized, double-blind comparisons assessing the safety and efficacy of CIN preventive measures (hemofiltration, N-acetylcysteine, or other drugs) in patients with preexisting renal failure [18–30]. Four studies were prospective, randomized comparisons of CIN incidence with different contrast agents [13, 14, 16, 17].

Forty-five full-text publications were excluded for any of the following reasons: incompletely reported renal laboratory data in terms of parameters and/or duration of follow-up; patient population with normal renal function or with baseline serum creatinine above 3.5 mg/dL; contrast medium not identified or pooled by class; number of patients receiving a specific contrast medium not reported; investigations with the ionic dimer ioxaglate; different end point used to define CIN.

RESULTS

A total of 1365 patients met the selection criteria. The baseline characteristics of the patients in the selected primary studies are shown in Table 2. In the NEPHRIC study, 100% of patients had both diabetes mellitus and mild-to-moderate renal insufficiency [16], while the percent of diabetic patients in the other studies ranged between 15% and 64%. Three studies included patients

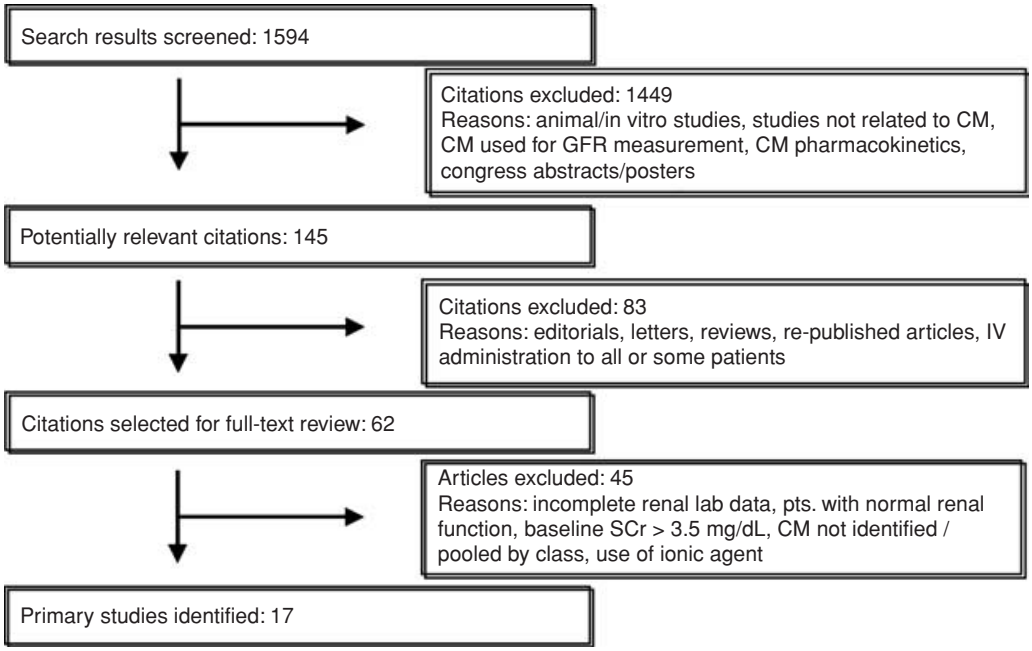

Fig. 1. Study selection diagram.

with more severe renal compromise [17, 23, 29]. There were differences in other baseline characteristics among the various CM tested. The iodixanol patients received slightly more contrast volume (162 vs. 139 mL all others) and had a greater percentage of diabetic patients (61% vs. 41% of all others), while iopamidol patients were less likely to have diabetes (35% vs. 49% all others), and the iopamidol and iohexol patients received less contrast volume (126–128 mL vs. 151 mL of all others). These differences were influenced by two individual studies involving iodixanol, the NEPHRIC study [16], which included 100% diabetics, and the RAPPID study [20], in which a high volume of contrast media was administered (222 mL).

Table 2 shows details about the hydration protocols and contrast exposure in the different primary studies. No data about hydration were available for the comparison between iodixanol and iohexol conducted by Chalmers et al [17]. In general, vigorous hydration was used in all the other studies, as recommended in patients with renal impairment. Doses of contrast were in general >100 mL, except in the study by Chalmers et al (53–60 mL for iohexol and iodixanol, respectively) [17] and in the study by Durham et al for iohexol (85 ± 42 mL) [19].

The CIN incidence in the different studies is reported in Table 3. CIN was defined as an absolute SCr increase of 0.5 mg/dL or above in 10 studies [13, 14, 17, 18, 21–23, 25–27]. Five studies used a relative SCr increase by 25% or greater as end point for CIN [20, 24, 27, 28, 31]. In most cases, the post-CM measurement of SCr occurred at 48 to 72 hours after the angiographic procedure [7, 13, 14, 17, 21–28, 31]. In two studies, SCr measurement was performed at 1 to 7 days following the intra-arterial administration of the contrast agents, and the maximum SCr value was used for CIN assessment [18, 20]. Overall, there were 230 cases of CIN in the primary studies involving 1365 high-risk patients (overall CIN incidence of 16.8%).

Table 4 presents the results of the logistic regression analysis. The adjusted odds ratios from the model showed that the risk of CIN is similar with iopamidol (OR 0.318, 95% CI 0.19-0.533) and iodixanol (OR 0.262, 95% CI 0.156-0.438). Both iopamidol and iodixanol showed a significantly lower risk of CIN compared to iohexol. Baseline SCr levels, CM volume, and age appeared to significantly increase the risk of CIN in the selected study population, while diabetes mellitus and gender distribution did not. All these factors were adjusted to keep consistency in the model so that the above comparison among contrast media more accurately reflected the true treatment effect on the incidence of CIN.

The incidence of CIN was 10% to 37% with iohexol [13, 16–19], 3% to 21% with iodixanol [16, 17, 20, 21], 6% to 25% with iopamidol [14, 22–24, 27, 30], 45% with ioxilan [25], 11% to 13% with iopromide [26], 20% with iomeprol [28], and 50% with iopentol [29] (Fig. 2).

No major differences were observed in the incidence of CIN (16.8% all studies) by excluding iopromide, iomeprol, or ioxilan from the group of the nonionic monomers because of the limited sample size of the studies with those agents (iopromide excluded: 214/1229, 17.4%; ioxilan excluded: 217/1336, 16.2%; iomeprol excluded: 220/1315, 16.7%). The exclusion of iopentol led to a more marked decrease in CIN incidence (from 16.8%

Table 2. Baseline patient characteristics, hydrations protocols, contrast dose, and CIN end point in the selected primary studies

Study	Study group[a]	Total number of patients with renal failure	Age yrs (mean ± SD)	M/F %	% Diabetes	Baseline SCr mg/dL (mean ± SD)	Baseline CrCl mL/min (mean ± SD)	Hydration protocol	Contrast agent dose mL (mean ± SD)	CIN end point
Rudnick et al, Kidney Int 1995 [13]	Iohexol	250	64 ± 11	71/29	41	1.9	NA	IV fluids at 100 mL/hr for at least 4 hrs before and 24 hrs after angiography	140 ± 57	↑ SCr ≥ 0.5 mg/dL at 48–72 hrs post-exam
Hans et al, Am Surg 1998 [18]	Control/ Iohexol	27	71 ± 8.2	89/11	37	1.9 ± 0.5	49 ± 17	Saline infusion 1 hour before arteriography and continuing for 12 hrs	140 ± 30	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Durham et al, Kidney Int 2002 [19]	Placebo/ Iohexol	41	70 ± 10	68/32	46	2.3 ± 0.5	NA	1 mL saline/kg b.w. IV, for 12 hrs before and 12 hrs after angiography	85 ± 42	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Chalmers et al, BMJ 1999 [17]	Iohexol	48	65	69/31	35	3.3	NA	NA	53	Max ↑ SCr ≥ 25% 24 hrs-7 days post-exam
Aspelin et al, N Engl J Med 2003 [16]	Iohexol	65	71 ± 9	54/46	100	1.6 ± 0.5	47 ± 17	Before angiography: 500 mL water orally, 500 mL saline IV; after angiography: 1L saline IV	162 ± 82	↑ SCr ≥ 0.5 mg/dL at 72 hrs post-exam
Aspelin et al, N Engl J Med 2003 [16]	Iodixanol	64	71 ± 6	64/36	100	1.5 ± 0.5	50 ± 13		163 ± 88	
Chalmers et al, BMJ 1999 [17]	Iodixanol	54	62	72/28	31	3.1	NA	NA	60	Max ↑ SCr ≥ 25% 24 hrs-7 days post-exam
Baker et al, JACC 2003 [20]	Placebo/ Iodixanol	39	71 ± 9	85/15	44	1.8 ± 0.4	44 ± 18	1 mL saline/kg b.w. IV, for 12 hrs before and 12 hrs after angiography	222 ± 162	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Boccalando et al, Cathet Cardiovasc Intervent 2003 [21]	Placebo/ Iodixanol	106	65 ± 11	56/44	57	1.9 ± 0.6	54 ± 37	75 mL/hr for 12 hrs before and 12 hrs after angiography	191 ± 120	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Taliercio et al, JACC 1991 [14]	Iopamidol	155	68	83/17	15	1.8	NA	Oral and IV fluids from the night before catheterization. Pericatheterization fluids individualized on the basis of clinical status.	134	Max ↑ SCr > 0.5 mg/dL 24 hrs-7 days post-exam
Kay et al, JAMA 2003 [22]	Placebo/ Iopamidol	98	69	63/37	36	1.4 ± 0.4	44 ± 12	1 mL saline/kg b.w., for 12 hrs before and 12 hrs after angiography	120	↑ SCr ≥ 25% at 48 hrs post-exam
Shyu et al, JACC 2002 [23]	Placebo/ Iopamidol	61	70 ± 7	66/34	64	2.8 ± 0.8	23 ± 8	1 mL saline/kg b.w. IV, for 12 hrs before and 12 hrs after angiography	115 ± 48	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Oldemeyer et al, Am Heart J 2003 [24]	Placebo/ Iopamidol	47	75 ± 8	55/45	49	1.7 ± 0.7	35 ± 13	1 mL saline/kg b.w. IV, for 12 hrs before and 12 hrs after angiography	127 ± 73	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Fung et al, Am J Kidney Dis 2004 [30]	Placebo/ Iopromide	45	68 ± 9	67/33	56	2.37 ± 0.6	28 ± 9	NA	121 ± 66	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Goldenber, Eur Heart J 2004 [27]	Placebo/ Iopamidol	39	69 ± 10	79/21	49	1.9 ± 0.3	41 ± 13	1 mL 0.45 saline/kg b.w. for 12 hrs before and 12 hrs after angiography	121 ± 49	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Diaz-Sandoval et al, Am J Cardiol 2002 [25]	Placebo/ Ioxilan	29	72 ± 2	90/10	38	1.6 ± 0.1	NA	1 mL saline/kg b.w. IV, for 12 hrs before and 12 hrs after angiography	189 ± 12	↑ SCr ≥ 25% or ≥ 0.5 mg/dL at 48 hrs post-exam
Briguori et al, JACC 2002 [26]	Placebo/ Iopromide	91	64 ± 9	89/11	32	1.5 ± 0.4	54 ± 16	1 mL saline/kg b.w. IV, for 12 hrs before and 12 hrs after angiography	200 ± 144	↑ SCr ≥ 25% at 48 hrs post-exam
Huber et al, Am J Cardiol 2003 [28]	Placebo/ Iomeprol	50	69 ± 10	78/22	34	1.7 ± 0.7	NA	Fluid supply ≥ 2 L/day, plus eventual additional hydration, if needed	78 ± 22	↑ SCr ≥ 0.5 mg/dL at 48 hrs post-exam
Marenzi et al, N Engl J Med 2003 [29]	Control/ Iopentol	56	69 ± 11	77/23	30	3.1 ± 1.0	26 ± 8	1 mL saline/kg b.w. IV, for 12 hrs before and 12 hrs after angiography	258 ± 132	↑ SCr ≥ 25% at 48 hrs post-exam

Table 3. Incidence of contrast-induced nephropathy (CIN), by contrast medium

Contrast medium	Total number of patients	Number of patients with CIN	CIN incidence (%)
Iohexol	431	93	21.58
All other (w/o Iohexol)	934	137	14.67
All other (w/o Iohexol and Iodixanol)	671	112	16.69
Iodixanol	263	25	9.51
All other (w/o Iodixanol)	1102	205	18.60
Iopamidol	400	45	11.25
All other (w/o Iopamidol)	965	185	19.17
All other (w/o Iopamidol and Iodixanol)	702	160	22.79
Other contrast media[a]	271	67	24.72
All contrast media	1365	230	16.85

[a]Iopromide, ioxilan, iopentol, and iomeprol.

Table 4. Logistic regression analysis: CM and baseline risk factors

Parameter	Coefficient estimate	*P* value	Odds Ratio and 95% CI
CM			
Iopamidol	−0.4011	0.0367	0.318 (0.19, 0.533)
Iodixanol	−0.5958	0.0019	0.262 (0.156, 0.438)
Other	0.2522	0.1295	0.611 (0.376, 0.993)
Iohexol	Reference		1.00
Age *years*	0.1052	0.0007	1.111 (1.045, 1.181)
Gender (% male)	−0.0042	0.7138	0.996 (0.974, 1.018)
Diabetes mellitus%	−0.00633	0.3349	0.994 (0.981, 1.007)
Baseline SCr *mg/dL*	0.3487	0.0217	1.417 (1.052, 1.909)
Volume of CM administered *mL*	0.00809	<.0001	1.008 (1.004, 1.012)

to 15.4%) because of the high rate of CIN in the study by Marenzi et al (28/56, 50%) [29]. It should be noted that the patients in that study had severe preexistent compromise of renal function (mean baseline SCr 3.1 ± 1.0 mg/dL; mean CrCl 26 ± 8 mL/min) and received very high doses of contrast (258 ± 132 mL on average).

Table 4 shows the incidence of CIN by CM. The incidence of CIN with iohexol was 21.6% (93/431). When the iohexol data were excluded, the CIN incidence dropped from 16.9% to 14.7% (137/934). The incidence of CIN with iohexol was significantly higher than the incidence of CIN with all the other agents (21.6% vs. 14.7%, $P = 0.0015$, RR 1.47, 95% CI 1.16-1.87). Also, the incidence of CIN with iohexol was higher compared to that observed with all the other nonionic monomers (21.6% vs. 16.7%, $P = 0.0419$, RR 1.29, CI 1.01-1.65).

The incidence of CIN with iopamidol was 11.3% (45/400). When the iopamidol data were excluded from the analysis, the CIN incidence following all the other nonionic agents went up to 19.2% (185/965). The incidence of CIN with iopamidol was significantly lower than the incidence of CIN with all the other agents (11.3% vs. 19.7%, $P = 0.0004$, RR 0.59, 95% CI 0.43-0.80). Also, the incidence of CIN with iopamidol was significantly lower than the incidence of CIN with all the other nonionic monomers (11.3% vs. 22.8%, $P < 0.0001$, RR 0.49, CI 0.36-0.67).

Significant differences were also observed between iopamidol and iohexol (11.3% vs. 21.6%, $P = 0.0001$, RR 0.52, 95% CI 0.38-0.72), and between iodixanol and iohexol (9.5% vs. 21.6%, $P < 0.0001$, RR 0.44, CI 0.29-0.67).

DISCUSSION

The results of our analysis suggest that differences in the incidence of CIN among contrast media cannot be explained solely by differences in CM osmolality. In a previous metaanalysis, Barrett el al found no difference in the incidence of CIN between agents of different osmolality except in those with preexisting renal insufficiency (creatinine >1.35 mg/dL or estimated GFR <70 mL/min). However, the Barrett analysis did not include any studies with iso-osmolality CM and did not take into account the level of renal insufficiency or the volume of CM administered [15]. The current analysis extends the range of CM to include iso-osmolality and attempts to control for additional risk factors, such as age, gender, presence of diabetes, volume of CM administered, and baseline SCr, which could independently contribute to the incidence of CIN.

The mechanism of CIN is multifactorial. Experimental studies suggest that CIN is due to both a direct toxic effect on the renal tubular epithelial cells and to contrast-induced renal medullary ischemia. The contribution of CM osmolality to the pathogenesis of CIN is unclear. Animal and in vitro experiments with hypertonic saline and mannitol support a role for hyperosmolality in causing direct renal cell injury and decreases in renal blood flow and GFR [32]. However, these studies were conducted with solutes at osmolalities >1500 mOsm/kg. More recent in vitro experiments with mannitol at osmolalities <1000 indicate a much reduced toxic effects relative to CM of the same osmolality [33–35]. These observations are supported by in vitro studies with different CMs. These studies suggest that factors other than osmolality (such as viscosity, hydrophylicity) may contribute to the toxic effect of CM [36–40]. It is noteworthy that iohexol was found to be more toxic than other nonionic monomers on proximal tubule vacuolization [41, 42] and capillary congestion [42]. The relationship of these histologic changes to the functional changes in RBF and GFR is unclear.

Our analysis suggests that iodixanol, an iso-osmolality agent (290 mOsm/kg), is associated with a lower incidence of CIN compared to iohexol (844 mOsm/kg) (see Table 2). However, iodixanol does not appear to be significantly less nephrotoxic than another low osmolality CM, iopamidol (796 mOsm/kg). Observed differences in the incidence of CIN with different CM were not explained by differences in patient age, baseline renal function, or

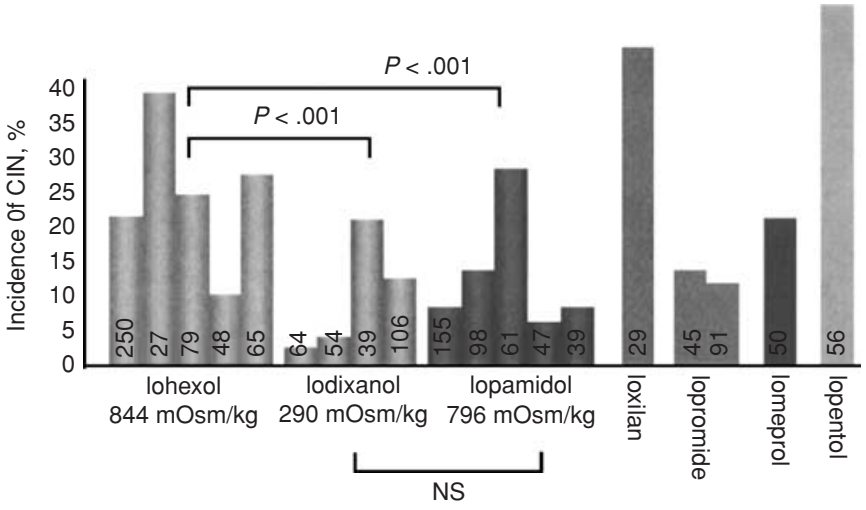

Fig. 2. Incidence of contrast-induced nephropathy in patients with chronic renal insufficiency receiving nonionic contrast agents in various prospective studies (iohexol, data extracted from [13, 16–19]; iodixanol, data extracted from [16, 17, 20, 21]; iopamidol, data extracted from [14, 22–24]; ioxilan, data extracted from [25]; iopromide, data extracted from [26]; iomeprol, data extracted from [27]; iopentol, data extracted from [28]).

volume of CM administered. This suggests that characteristics of the individual contrast agents in addition to osmolality may be important in causing nephrotoxicity. This conclusion is supported by animal studies that have found that the direct tubular toxicity of iohexol is significantly greater than that of iopamidol and other CM of similar osmolality [41, 42]. In our analysis, iohexol was indeed associated with a higher incidence of CIN compared to all other low osmolality agents (21.6% vs. 16.7%, $P < .0.0419$).

The viscosity of the contrast solution may play an additional role in contributing to the fall in glomerular filtration rate and renal medullary blood flow. It has been suggested that the higher viscosity of iodixanol may cause a reduced transit time of these agents in the renal tubules and subsequent increased tubular pressures, which in turn can cause a decrease in glomerular filtration rate [39]. The iso-osmolality nonionic dimers have been reported to cause more red blood cell aggregation and cessation of flow in the renal microcirculation [43], and more reduction in medullary renal blood flow [36, 37] than hyperosmolality agents in animal models. It may be that both osmolality and viscosity contribute to nephrotoxicity. This may explain why iodixanol, a CM isotonic to human plasma but with a high viscosity, has a similar incidence of CIN compared to iopamidol, a CM hypertonic to plasma but with a low viscosity. It may also explain why iohexol has a higher incidence of CIN relative to iopamidol.

LIMITATIONS

This analysis is not a traditional meta-analysis made up of randomized comparisons between two treatment groups. We attempted to identify all available studies referencing the rate of CIN with the use of a single CM. As such, we included studies that were not randomized comparisons between two different CM. Such head-to-head comparison studies have the advantage that the randomization process should distribute known and unknown confounding variables equally. This strengthens any conclusion that differences in the incidence of CIN are attributable to the CM. Without the benefit of such a randomization procedure, we attempted to account for the known confounders by meta-regression using study level mean data. The strength of this approach is that it accounts for the most well-known risk factors for CIN.

Although we attempted to adjust for the known risk factors for CIN (age, presence of diabetes mellitus, degree of baseline renal insufficiency, volume of CM administered), we could not account for possible interactions between these risk factors. Most of the patients in this analysis underwent cardiac angiography or interventions, so it is likely that the highest concentration of iodine (mgI/mL) available for each agent was used. However, several studies did not reference the concentration of the CM used. Finally, because we analyzed studies employing intra-arterial injection of CM, this analysis does not address potential differences among CM in the risk of CIN following their intravenous administration.

CONCLUSION

Meta-regression analysis of the available data on the incidence of CIN in high-risk patients following intraarterial administration of low- or iso-osmolality CM suggests that the osmolality of the contrast agent alone does not account for the differences in the incidence of CIN. While earlier data suggested a role for osmolality in the pathogenesis of CIN at high osmolalities (>1000 mOsm/kg), our analysis suggests that either osmolality in the range of 290 to approximately 800 is not toxic to the kidney, or that for CM within this range of osmolality other characteristics of CMs, such as viscosity or direct molecular toxicity, play a greater role in the development of CIN. Future prospective clinical trials comparing individual

low- and iso-osmolality CMs in high-risk patients will help to further explore the role of osmolality and viscosity in CIN.

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