"Allergic-like" reaction risk in patients undergoing non-intravenous contrast urography

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MOSES RA, VOLLSTEDT AJ, PAIS VM JR. "Allergic-like" reaction risk in patients undergoing non-intravenous contrast urography. *Can J Urol* 2018;25(6):9601-9605.

Introduction: *Though widely performed, the safety of non-intravenous contrast (NIVC) urography in patients with documented intravenous, iodinated contrast allergic like reactions (ICA) is unclear. The purpose of this study was to determine the risk of "allergic-like" reaction (ALR) events in patients with ICA undergoing NIVC urography.*
Materials and methods: *Patients undergoing contrast urography at a single institution were identified between 2011-2014. Patient charts were reviewed for documented ICA prior to index surgery, preoperative allergy prophylaxis with steroid or antihistamine, and acute allergic reactions identified by ICD codes within 24 hours of surgery.*
Results: *A total of 2,650 patients were included, 1,325 female (50%). Of these patients, 113 (4.2%) had an ICA. Overall 33% (37/113) of patient received preoperative allergy prophylaxis with a steroid or antihistamine. A potential ALR related ICD-9 code was identified in one patient (0.8%) with a prior IVC ALR without allergy prophylaxis within 24 hours preoperatively undergoing percutaneous nephrolithotomy (PCNL). This event was found to be an associated with a myocardial infarction and lacked ALR sequelae.*
Conclusion: *Despite commonly voiced concerns, in this large series of over 2,500 patients, including 113 patients with a prior history of ICA undergoing contrast urography, only one patient was found to have a potential ALR event following PCNL. No patients undergoing a retrograde contrast urography with prior, documented ICA had a NIVC ALR event despite a low rate of pretreatment with corticosteroid or antihistamine.*

Key Words: iodinated contrast "allergy-like" reaction, urography, endourology

Introduction

Non-intravenous contrast (NIVC) urography is a frequently performed urologic procedure[1] yet little is known regarding procedure related rates of "allergic-like" reactions (ALR). Intravenous iodinated contrast (ICA) ALRs are well described events during intravenous contrast administration, however, are relatively infrequent.[2] Described manifestations of ALR following contrast administration include shortness of breath, wheezing, respiratory distress, and urticaria[3] and often lack an identifiable antigen-antibody response.[4] Mild ALR have been reported in up to 0.2% to 17% and severe ALR in 0.02% to 0.5% of the population,[5] with only 1/10,000 patients suffering potentially ALRs[6] due to the urothelium preventing significant systemic absorption.[7-9]

Prior studies have evaluated contrast related ALRs using older contrast mediums. It is well established that potential contrast medium side effects vary by generation[1,2,10] with older generations having high risk, high-osmolar ionic monomers and newer generations

Accepted for publication September 2018

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(second and third) having low risk, low osmolality, non-ionic monomers with low rates of systemic diffusion.[3] Uncertainty regarding risk of contrast reactions may lead providers to pre-medicate patients undergoing NIVC administration with steroids and antihistamines despite associated risks and lack of level one evidence.[4] Contemporary studies regarding the rate of such reactions in NIVC administration with second generation contrast agents are lacking. The purpose of this study was to evaluate our institutional incidence of ALR events in patients with prior ICA undergoing NIVC urography.

Materials and methods

A retrospective, electronic medical record chart review was performed of all patients undergoing urologic procedures requiring use of contrast media/urography between April, 2011 and August, 2014 at a single academic medical center. This study was submitted and approved by the local institutional human subjects' committee review board. Patients less than 18 years of age were excluded from the study.

The specific procedures included retrograde only (retrograde pyelogram, stent placement, ureteroscopy) and retrograde + antegrade procedures [percutaneous nephrolithotomy (PCNL)]. The patients' electronic charts were reviewed for documented ICA prior to the index procedure date. This included ALRs to iodine containing mediums including IV contrast. These charts were additionally reviewed for premedication within 24 hours of the procedure with either corticosteroids or antihistamines. Further, the charts of patients possessing ICA were reviewed for "allergic-like" sequelae within 24 hours of the event using ICD-9 codes including: "allergic reaction "995.3, "anaphylaxis" 995.0, "drug reaction" 995.27, "urticaria/hives" 708, "bronchospasm" 519.1, "laryngeal edema" 478.6, "acute respiratory failure" 518.8, "acute respiratory distress" 518.5, 518.82, "reintubation" 967, "hypotension" 458.0, and "tachycardia" 785.0, Figure 1. Patients were then further broken down into retrograde only procedures and antegrade procedure (PCNL) groups to determine rate of prophylaxis and anaphylactic related events. On average, patients received 10 mL to 40 mL of Iohexal (omnipaque) (30 mg/mL) diluted 1:1 with normal saline which was used for all procedures. In all instances, contrast was used to opacify the collecting system for procedural anatomical mapping.

Results

A total of 2,560 patients underwent contrast urography during the 40 month study period, in a population 52% (1,325/2,560) female with an average age 58 yrs (+/- 18yrs). Of these, 113 (4%) had a listed ICA prior to the index procedure. There was no difference in age, gender, and rate of comorbidities (asthma, chronic obstructive lung disease, coronary artery disease) between groups. Interestingly, patients with a listed ICA were more likely to have diabetes and a documented psychiatric disorder, Table 1.

Thirty-one percent (35/113) of the ICA cohort received allergy prophylaxis with a steroid or antihistamine. On full chart review, only one patient had a suspected ALR event within 24 to 72 hours of the procedure and carried the ICD-9 code of "acute respiratory failure" 995.3, Figure 1. On further review, this patient had undergone a PCNL and had a significant past cardiac history. The patient's prior ICA was noted during the surgical time out. No antihistamine or corticosteroid was administered preoperatively. The PCNL was carried out in the prone position with both antegrade and

TABLE 1. **Patient comorbidities**

Prior IV contrast allergy-like event	**No (n = 2447)**	**Yes (n = 113)**	**p value**
Female gender	51% (1257/2447)	60% (68/113)	0.068
Asthma	8% (200/2447)	13% (15/113)	0.079
Coronary artery disease	12% (308/2447)	17% (19/113)	0.194
Chronic obstructive pulmonary disease	7% (173/2447)	11% (13/113)	0.092
Renal disease	12% (300/2447)	14% (16/113)	0.558
Diabetes	13% (319/2447)	42% (47/113)	< 0.001*
Psychiatric disorder	2% (59/2447)	12% *14/113)	< 0.001*

*p value < 0.05

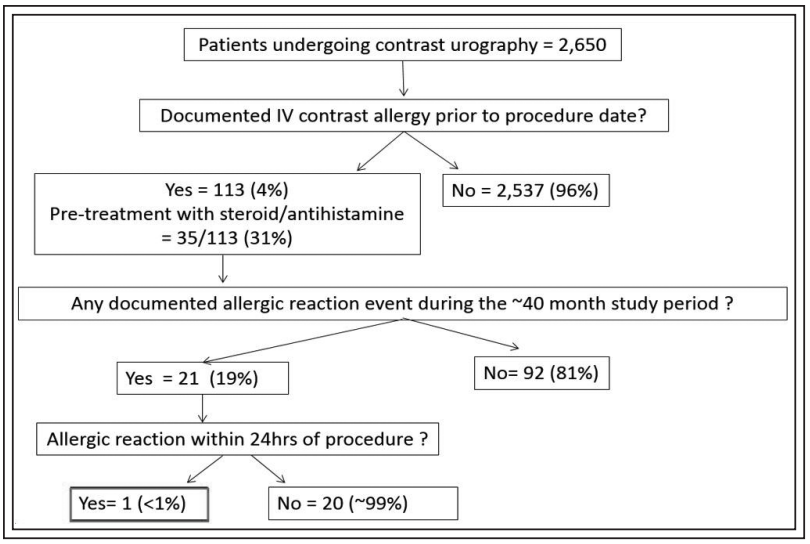

Figure 1. Study design.

retrograde contrast administration for collecting system opacification. A single lower pole access was obtained and a 300-milliliter blood loss was recorded. The patient remained stable from hemodynamic and pulmonary standpoint throughout the operative case, was extubated postoperatively, and transferred to the recovery area without a known complication. Approximately 1 hour after reaching the recovery area, the patient complained of "chest pressure". The patient received supplemental oxygen therapy during this period (prompting above ICD-9 coding) and was ultimately found to have an anterolateral myocardial infarction without associated arrhythmia or hemodynamic instability. No invasive cardiac intervention was required, thus qualifying as a Clavien Grade 1 complication.[11] No subsequent steroid was administered, and this event was not clinically considered to be allergic-like. The patient was managed conservatively and ultimately discharged to home on postoperative day five.

When analyzing our contrast procedure groups further, Table 2, 88% (100/113) underwent retrograde upper tract interventions (ureteroscopy, stent placement, or retrograde pyelogram) and 12% (13/113) underwent PCNL. The percentage of patients receiving preoperative allergy prophylaxis including preoperative steroid or antihistamine within each group was 32% (32/100) in the ureteroscopy group and 38% (5/13) in the PCNL group. No definite ALR event occurred during the study period.

Discussion

Similar to prior case series, our data demonstrate a very low rate of potential ALR in all patients with documented prior ICA undergoing NIVC urography. Despite a low rate of prophylactic premedication of 32% in the retrograde pyelogram group, no patients had a documented ALR.

Frequently, patients with ICA undergo retrograde or antegrade contrast urography, without ALR due to limited systemic absorption rates.[7,8] In 1970, Castellino and Marshall sought to determine if non-hydronephrotic kidneys as compared to the hydronephrotic kidneys would allow passage of contrast medium into systemic circulation. Using 15 adult dogs, they demonstrated with low pressure administration of radioactive diatrizoate only approximately 1.0% could be found in the blood and 1.93% to 6.9% in the contralateral kidney urine for up to 2 hours.[7] A follow up study by Marshall to determine ureteric absorption of continuously infused contrast reported a systemic contrast absorption of only 1% with perfusion time of 2 hours, and a negligible 0.1% with a perfusion time of 30 minutes.[9]

TABLE 2. **Patients with listed iodinated contrast allergy-like event prior to index procedure**

Surgery type	**n**		**Prophylaxis (steroid/antihistamine)**		**AALR within 24hrs**	
*Retrograde access only	100	88%	32	32%	0	0%
PCNL	13	12%	5	38%	**1	8%
Total	113	100%	37	33%	1	1%

*retrograde pyelogram, stent placement, or ureteroscopy only
**patient did not receive premedication with steroid or antihistamine
ALAR = acute allergy-like reaction; PCNL = percutaneous nephrolithotomy

Extrapolating this to real time contrast urography, in which contrast is usually in contact with the mucosa for only a matter of seconds to minutes, these absorption parameters would likely be considerably lower. Of note, they revealed absorption may be greater in the hydronephrotic or obstructed kidney or in cystography in which the contrast is not immediately drained.[9]

Another retrospective study by Maluf et al evaluating NIVC absorption demonstrated that enough of a first generation contrast could be absorbed through the urothelium to yield a pyelogram.[12] Similarly, Currarino et al showed that children undergoing VCUG could also form an excretory urogram if the contrast was left long enough.[13] In contrast to our study, these patients were undergoing cystograms as opposed to low volume, upper tract contrast administration. Further, both of these studies were performed on patients with delayed bladder emptying and with older ionic, high-osmolar agents; however, systemic absorption potential should be kept in mind when performing large volume contrast administration in an obstructed collecting system.

In a 1980 a study evaluating ALR, Johenning reported two cases of "allergy-like" reactions including wheezing and hypotension after retrograde pyelogram performed with the first generation, ionic, high osmolar contrast agents.[14] Both patients carried a prior diagnosis of ICA and neither had evidence of extravasation or backflow on intraoperative films. Interestingly, the pyelograms were performed while the patients were awake, however ALR had not occurred on prior retrograde pyelograms performed under anesthesia. Both patient reactions were addressed with antihistamines and corticosteroids without further sequelae. The authors suggested that consideration should be given to possible events in patients with ICA, although such events were rare, even with first generation contrast agents.

In one of the largest studies to date, Weese et al performed a retrospective review of 783 consecutive voiding cystourethrography (VCUG) (320) and retrograde pyelograms (463).[15] Similar to prior reports, there was a low rate of events with two suspected ALR, both in patients undergoing VCUG with first generation contrast agents. Neither patient had prior documented ICA, however developed an immediate ALR of a first generation, high osmolar ionic iothalamate meglumine (cysto-Conray) without evidence of bladder contrast extravasation. One patient underwent work up for suspected bladder neck obstruction and was found to have high grade vesicoureteral reflux after instillation of first generation iothalamate meglumine (cysto-Conray). The patient developed tachycardia, hypotension, and syncope. These symptoms were self-limited without pharmacotherapy administration after being placed in the Trendelenburg position. In their large series, the rate of ALRs was 0.26%. In contrast to our study, both events happened in patients undergoing VCUG. Similarly, no patients undergoing upper tract urography experienced ALRs. Unlike the Weese et al, we did not include VCUGs in our study, which possibly accounts for our differences. Further, all of the patients in our series received Iohexal (omnipaque) which may be better tolerated than the older, high osmolar compounds used in several of the prior studies cited.

These case series demonstrate a very low rate of ALR events in patients undergoing retrograde urography. Importantly, the majority of these reviews described patients undergoing urography with older, ionic, higher osmolar agents that have been associated with higher complication profiles as previously discussed.[2,4,6,10] Nevertheless, in contrast to prior studies, a more recent case report by Armstrong et al in 2005 demonstrated an ALR event with the use of second generation contrast agent, iohexol in a patient with a prior ICA who was pre-medicated with a steroid and antihistamine.[16] The patient reportedly underwent cystoscopy, retrograde pyelogram, and bladder biopsy for work up of hematuria. Despite reportedly normal upper tract anatomy without evidence of obstruction, the patient required transient reintubation for respiratory distress. In contrast to prior studies and ours, this patient did undergo a bladder biopsy following the retrograde urography which may have compromised the purported urothelial barrier. Of note, per our review, this is the only recent study or case report demonstrating a possible ALR event following non-intravenous urography with a second-generation iodinated contrast agent.

The one potential ALR event in our series occurred in a patient undergoing PCNL without premedication, however, it does not appear that the patient's respiratory failure was directly related to their contrast allergy but rather related to their cardiac event as they did not demonstrate the classic ALR sequelae, nor urticarial rash. It is unclear from this chart review whether the patient's prior ICA of hives occurred with an older hyperosmolar contrast agent. It should be noted that this patient did not receive premedication with corticosteroids or antihistamines prior to PCNL, a procedure that inherently exposes iodinated contrast agents to the blood stream due to the highly vascular access path. This may suggest that urologists should pay increased attention to contrast allergies in patients undergoing PCNL.

This study was limited by the inherent properties of a retrospective review. Subsequently, we could

not obtain granular detail regarding details of patients' prior ICA or confirmatory allergy testing. This study did not use imaging data to demonstrate characteristics of obstruction (hydroureteronephrosis) or extravasation. This was due to lack of uniform imaging storage for included cases in which contrast urography was performed. Lastly, we did not include allergic reactions of patients that did not have a prior ICA listed due to the parameters of the initial data collection. Despite these limitations, we demonstrated a low rate of potential ALR to NIVC urography in patients with documented ICA.

Conclusion

In our institutional review, one of the largest series to date of over 2,500 procedures, we found a very low rate of anaphylactic-like reactions following NIVC urography. A single potential contrast ALR event occurred in a patient undergoing percutaneous nephrolithotomy without allergy prophylaxis, however, on further review this seemed unlikely related to contrast administration. No patients undergoing isolated NIVC retrograde urography had a documented ALR event, despite a low rate of allergy prophylaxis. These findings suggest that that the risk of ALR from antegrade urography is low, and risk from retrograde urography is likely even lower. Further prospective studies are warranted to assess whether there is any benefit to prophylactic premedication in patients undergoing simultaneous antegrade and retrograde contrast administration. □

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