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SPECIAL ARTICLE

The prevention of contrast-induced nephropathy in Dutch hospitals

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Background: A major adverse effect of intravascularly administrated iodinated contrast medium is contrast-induced nephropathy (CIN). To reduce CIN incidence, two different prevention guidelines have been introduced in the Netherlands.

Objective: Our goal was to assess the use of CIN prevention guidelines at the radiology departments in Dutch hospitals.

Methods: We conducted a survey in all 90 Dutch hospitals with a radiology department. The questionnaire included questions about guideline execution (e.g. which guideline, (compliance) problems).

Results: All responding (67/90) hospitals used a CIN prevention guideline. When asked who was responsible for conducting preventive measures in high-risk patients identified according to either guideline, the referring physician was responsible in 38 hospitals (56.7%); in 23 hospitals (34.3%) there was a specialised CIN outpatient clinic. Renal function was routinely checked after exposure to intravenous iodinated contrast medium in all CIN outpatient clinics (23) and radiology departments (2) when these were responsible for this measurement and in 52.6% (18/38) hospitals when the referring physicians were responsible. When asked if identifying patients at risk caused any problems, 47.8% reported problems.

Conclusion: In all responding Dutch hospitals a CIN prevention guideline was used. There was considerable variation in the execution of the guidelines and there were substantial compliance problems. The follow-up procedure was more consistent in hospitals with an outpatient clinic.

KEYWORDS

Compliance, contrast-induced nephropathy, guidelines, prevention

BACKGROUND

The use of intravascular iodinated contrast media in radiological procedures has increased over the years.[1-3] Unfortunately the use of intravascular iodinated contrast medium is associated with contrast-induced nephropathy (CIN) and is one of the top three causes of acute nephropathy in hospitalised patients.[4] CIN is mostly defined as a rise of serum creatinine (SCr) of at least 25% or 44 μmol/l compared with the baseline with no other explanation for the rise in SCr or nephropathy. CIN usually develops within 24-48 hours after exposure to intravascular iodinated contrast medium and it seems to be transient in most cases. However, in some cases it is associated with long-term adverse events leading to increased morbidity and mortality.[4-9] The precise pathophysiology of CIN is unknown. It is a common theory that CIN is the result of transient vasoconstriction that leads to hypoperfusion of the glomeruli. This generates oxidative stress in combination with the nephrotoxicity of the contrast medium itself.[10-13]

During the past years, it has become clear which patients are at risk to develop CIN and what might be the best means of prevention in the patients at risk.[8,13-19] In general, patients with pre-existent kidney disease in combination with other risk factors (e.g. diabetes, hypertension) seem to be at risk for developing CIN. Oral and intravenous hydration before and after the contrast-enhanced examination in these at risk patients seems to reduce the incidence of CIN.[2,5,11,15-20]

The Dutch hospital patient safety program (Veiligheids Management Systeem: VMS) identified CIN as one of the ten main causes of preventable mortality and morbidity in Dutch hospitals and introduced a CIN prevention guideline in 2009.[21] The VMS prevention guideline for CIN is partly based on the multidisciplinary evidence-based CIN prevention guideline that was developed under the chair of the Radiological Society of the Netherlands (NVvR)

and introduced by the Dutch Institute for Healthcare Improvement (Centraal Begeleidings Orgaan: CBO) in 2007. [21-22]

These guidelines only differ in their strategy to identify patients at risk. The VMS guideline indicates that the estimated glomerular filtration rate (eGFR) should be determined in every patient scheduled for intravascular iodinated contrast medium administration. In case of an abnormal eGFR, other risk factors should be checked to identify patients at risk. The CBO guideline advises that risk factors should be assessed first and if present, eGFR has to be determined to identify patients at risk.

In both guidelines the prevention measures are similar and encompass prophylactic intravenous hydration before and after the procedure and discontinuation of metformin and all nephrotoxic medication. Two to three days after the intravascular contrast medium exposure, renal function should be verified (*see figure 1* and *tables 1* and *2*).

The introduction of these guidelines into clinical practice has led to discussion about the necessity of extensive prevention guidelines, feasibility and associated costs.

General critics were that the identification of high-risk patients and the measures that should be taken according to these guidelines are based on an overestimation of the incidence of CIN (especially for intravenous iodinated contrast medium administration) and therefore cause unnecessary use of medical resources.[23-25] However, others find that there is enough evidence and that the problem is often trivialised. They find these precautions have a great effect on the incidence and adverse outcomes of CIN.[2, 26,27]

Figure 1. *Patient flow in accordance with both guidelines*

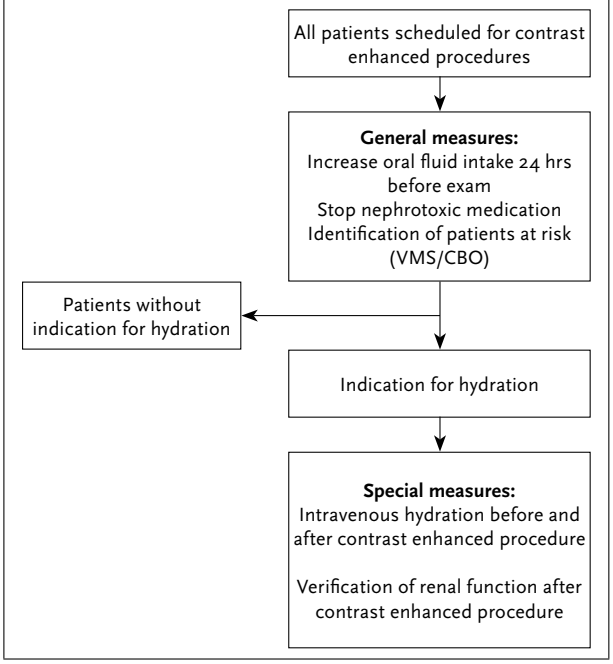

Table 1. *CBO: indication determination eGFR*

Risk factors (CBO)
Age > 60 years
Diabetes mellitus
Cardiovascular disease
Hypertension
History of urological or nephrological disease
Multiple myeloma or Waldenström's disease with small chain proteinuria
Use of nefrotoxic medication e.g. NSAID's*, metformin, aminoglycosides

***Non-steroidal anti-inflammatory drugs.**

Table 2. *Identification of patients at risk to develop CIN according to VMS and CBO guideline*

High-risk patients VMS guideline	**High-risk patients CBO guideline**
eGFR <60 ml/min and Diabetes Mellitus	eGFR <60 ml/min and diabetes mellitus
eGFR 45-60 ml/min and >1 risk factors: Peripheral arterial disease Congestive heart failure Age >75 years Anaemia: haematocrit (0.39 (m) 0.36 (f)[¥] Symptomatic hypotension Contrast volume >150 ml Decreased effective circulating volume Nephrotoxic medication i.e. diuretics and NSAIDs	eGFR <60 ml/min and >1 risk factors: Peripheral vascular disease Congestive cardiac disease Age >75 years Anaemia: (haematocrit <0.39 (m), <0.36 (f)), Symptomatic hypotension High volume (contrast index >1*) Dehydration Use of diuretics and/or NSAIDs, metformin, aminoglycosides
eGFR 45-60 mL/min and multiple myeloma/ Waldenström's disease with small chain proteinuria	eGFR <45 ml/min
eGFR < 45 ml/min	

[¥]**m=male, f=female, *contrast volume in relation to body mass index.**

Given these varying opinions and no uniform national guideline, one might envision a considerable variation in implementation of CIN prevention.

We aimed to assess whether Dutch hospitals used a CIN prevention guideline in contrast-enhanced procedures performed at the radiology departments. If they did, on which of the two Dutch guidelines this was based and if there were problems with the compliance of the prevention guideline. We also tried to assess whether the implementation of the guidelines was the same in every hospital.

METHODS

Questionnaire

A survey was performed using a questionnaire (*see appendix 1*) which was sent by email to radiologists in

all Dutch hospitals. Since radiologists mainly have a central role in the implementation of these guidelines, we addressed radiologists who where specifically involved with the prevention of CIN in their hospital. The questionnaire included questions concerning the CIN prevention guideline that was followed, who (e.g. the referring physician, radiology department) was responsible for the execution of the guideline, whether implementation of the guideline had led to any kind of problems and whether renal function was measured before and after an intravascular iodinated contrast enhanced procedure. Furthermore, we included some general questions, including information about the hospital (*appendix 1*). The survey was performed between May and August 2012.

Response

After two weeks all non-responders were contacted. They initially received a reminder via e-mail that – in case of no response – was followed by a phone call. We aimed to obtain a response rate of at least 70%. Of the hospitals that did not respond after two reminders, we decided post hoc to check whether they used a prevention guideline and which guideline; we did this to ensure that we did not overestimate the use of one of the two CIN prevention guidelines. We checked this by looking up information on the hospital's website. If the information on the website did not give clear details about the CIN prevention in the radiology department (e.g. which guideline was used and if and when eGFR was determined) we contacted the radiology department by phone. We did not try to complete the information of the non-responding hospitals for the other parts of the questionnaire.

Data presentation

We used descriptive statistical analysis to summarise the results. Categorical data were expressed as numbers and percentages. We used IBM® SPSS® statistic data editor version 19 SPSS® inc. to summarise the results.

RESULTS

General information

Of the 90 hospitals that were contacted, 67 (74.4%) responded, including all eight academic hospitals. The smallest hospital that participated had 140 beds, the largest hospital 1339 beds.

Guideline used

All responding hospitals used a prevention guideline; most hospitals (97.0%; 65/67) used either the VMS or CBO guideline. The VMS guideline had been adopted in the majority of hospitals (70.1%; 47/67) and a minority followed the CBO guideline (18/67; 26.9%). In two hospitals (3.0%; 2/67) a combination of the VMS and CBO guideline was used.

In 23 hospitals an outpatient clinic specialised in CIN prevention had been installed, these mainly (87%; 20/23) concerned hospitals using the VMS guideline.

Non-responders

All 23 non-responding hospitals had a prevention guideline. Most hospitals (65.2%; 15/23) used the VMS guideline, 21.7% (6/23) used the CBO guideline and the remaining (8.7%; 2/23) hospitals used a combination or variation of the two guidelines *(table 3)*.

Estimated glomerular filtration rate

Both VMS and CBO guidelines advise to determine the eGFR by using the Modification of Diet in Renal Disease (MDRD) formula in order to identify patients at risk. Renal function was determined in compliance to the guideline (MDRD-4 point formula) in 76.1% (51/67) of the hospitals, 6.0% (4/67) used the MDRD-6 point formula, 7.5% (5/67) the Cockcroft-Gault and 10.4% (7/67) of the hospitals used another not further specified formula (*table 4*).

Responsibility for general measures

Both guidelines also describe the general measures which are applicable in every patient receiving intravascular iodinated contrast medium. These include advising the patient to drink extra fluids, instructing the patient what to do if dehydration, diarrhoea or hospitalisation occurs in the time between the request for the examination and the examination itself. If patients use diuretics or non-steroid anti-inflammatory drugs (NSAIDs) they should be advised to stop these 24 hours in advance.

In most hospitals, 74.6% (50/67), the referring physician was responsible for the general measures, followed by the

Table 3. *Guidelines used in different Dutch hospitals*

Guidelines used	**N= 67**
Response % ***(n)***	74.4 (67/90)
Hospitals that followed guideline % ***(n):67***	
VMS	70.1 (47)
CBO	26.9 (18)
Other	3.0 (2)
Specialised outpatient clinic % ***(n): 23***	
VMS	87.0 (20)
CBO	13.0 (3)
Other	
Non-responding hospitals % ***(n): 23***	
VMS	65.2 (15)
CBO	26.1. (6)
Other	8.7 (2)

Table 4. *Variation in execution of the guidelines*

Variation in execution	**N=67**
eGFR % *(n)*	
MDRD-4 point	76.1 (51)
MDRD-6 point	6.0 (4)
Cockroft-Gault	7.5 (5)
Other	10.4 (7)
Responsible for implementing general measures % *(n)*	
Radiology/ nuclear imaging department	3.0 (2)
Requesting physician	74.6 (50)
Outpatient clinic	16.4 (11)
Other	6.0 (4)
Responsible for specific patients at risk % *(n)*	
Radiology/ nuclear imaging department	3.0 (2)
Physician	56.7 (38)
Outpatient clinic*	34.3 (23)
Other	9.0 (6)
Determination of renal function % *(n)*	
No determination	28.4 (19)
Determination	71.6 (48)
Determination of renal function % *(n) by department*	
Radiology/ nuclear imaging department	100 (2/2)
Requesting physician	52.6 (20/38)
Outpatient clinic	100 (23/23)
Other	75 (3/4)

***Two outpatient clinics discussed specific measures with requesting physician**

specialised outpatient clinic in 16.4% (11/67), the radiology department in 3% (2/67) and four 6% (4/67) hospitals indicated having a different arrangement (*table 4*).

Responsibility for specific measures in patients at high risk

The responsibility for execution was different with respect to the enforcement of the specific, more intricate measures for patients identified as being at risk (e.g. intravenous hydration, verification of the eGFR after intravascular iodinated contrast medium exposure). The referring physician was responsible in 56.7% (38/67) of the cases and more hospitals indicated to have a specialised outpatient clinic (34.3%; 23/67), two hospitals with outpatient clinics indicated that after the need for specific measures was established the outpatient clinic discussed this with the referring physician. There were two radiology departments (3%) responsible and four other departments conducted these measures in the remaining 6% (4/67) (*table 4*).

Determination of renal function

To identify those patients who developed CIN, renal function has to be determined preferably within 48-72 hours after intravascular iodinated contrast medium exposure as is advised in the guidelines. In 48 hospitals renal function (eGFR) was determined after iodinated intravascular contrast administration. However, in 19 hospitals (28.4%; 19/67) renal function after intravascular contrast administration was not determined. All specialised outpatient clinics (23/23) screened for changes in renal function after iodinated intravascular contrast administration, as did the radiology departments (2/2). In hospitals where the referring physician was responsible for implementing the special measures, the majority (52.6%; 20/38) determined renal function after iodinated intravascular contrast administration. In the group of hospitals that reported having other arrangements regarding the responsibility of the implementation of special measures, most of them (75%; 3/4) determined renal function after intravascular contrast administration (*table 4*).

The time interval between intravascular iodinated contrast medium administration and renal function determination varied from two to seven days. Nine (13.4%; 9/67) hospitals determined renal function within the given interval of 48-72 hours.

Problems concerning selection of high-risk patients

When we asked responders about problems with the identification of patients at risk, 47.8% (32/67) reported that there were process-related problems in their institute. When we divided the hospitals according to which guideline they used, 48.9% (23/47) of the responders using the VMS guideline reported problems with the identification of patients at risk *vs* 50.0% (9/18) of the responders using the CBO guideline (*table 5*).

Most reported comments in the free text box were that the referring physicians did not determine the renal function prior to the requested procedure or did not mention whether other risk factors were present (26.8%; 18/67 responders). About 35% (24/67) of the responders also reported that some physicians might be trying to bypass the guidelines by not mentioning risk factors that

Table 5. *Problems concerning execution of guidelines*

Problems execution/compliance	**N=67**
Problems in selection high-risk patients % *(n/total)*	
All hospitals	47.8 (32/67)
VMS	48.9 (23/47)
CBO	50.0 (9/18)
Problems with general and specific measures % *(n/total)*	
All hospitals	43.3 (29/67)
VMS	48.9 (23/47)
CBO	33.3 (6/18)

later proved to be present or simply forgetting to identify patients at risk to develop CIN. Four responders reported that discontinuation of nephrotoxic medication was a problem in their institutes (*table 5*).

Problems concerning general and specific measures

When we asked about the application of the general and specific measures, 43.3% (29/67) reported that there were problems; this was somewhat higher in hospitals using the VMS strategy compared with the CBO strategy: 48.9% (23/47) *vs* 33.3% (6/18) (*table 5*).

The main problems were that there was no verification if preventive measures were executed (25.4%; 17/67 responders). If no preventive measures had been performed, this was in most cases discovered on the day of the intravascular iodinated contrast medium enhanced examination, leading to ad hoc logistical problems. These 17 responders (25.4%; 17/67) also reported that there was no agreement about who was responsible for determination of renal function after intravascular iodinated contrast medium administration, which made the determination of CIN unclear.

CIN incidence

We asked hospitals to report the CIN incidence in their institute. Forty-three (64.2%; 43/67) responders answered this question. The other 24 (35.8%; 24/67) hospitals did not answer this question.

Thirteen (19.4%; 13/67) hospitals reported that CIN did not occur in their institute, five (38.5%; 5/13) responders stated that this number was measured, the other eight (61.5%, 8/13) indicated this was an estimation.

Six (9%; 6/67) hospitals reported the incidence in percentages, varying from <1% up to 5%; three of the six (50%; 3/6) hospitals based this number on measurements; the other half estimated the incidence (50%; 3/6).

Of the three hospitals that measured the incidence in their institute, one reported that this was the incidence in outpatients who were identified as being at risk (incidence: 3%), one responder stated that the group of patients consisted of outpatients undergoing CT scans (incidence: 1.4%) the other respondent did not specify, one hospital derived their data from emergency department patients undergoing CT-pulmonary angiography who were clinically suspected of pulmonary embolism (incidence: 4%).

The remaining 24 hospitals did not provide exact information from which the incidence in percentages could be derived and compared, but the range varied from 0 up to 29 patients per hospital per year. Seven responders (29.2%; 7/24) declared that these numbers were measured and 17 (70.8%; 17/24) declared the numbers were estimated. The hospital that counted 29 cases in the past 12 months looked for other reasons for nephropathy besides CIN (*table 6*). They found other reasons in 28 cases reducing the cases of CIN to one.

Table 6. *Reported CIN incidence*

CIN incidence	**N=67**
Response % *(n/total)*	
Answered the question	64.2 (43/67)
Did not answer the question	35.8 (24/67)
Hospitals reporting incidence of 0%	19.4 (13/67)
Measured	38.5 (5/13)*
Estimated	62.5 (8/13)*
Hospitals reporting incidence in percentage % (n/total)	9(6/67)*
Range %	<1-5
Measured	50(3/6)*
Estimated	50(3/6)*
Hospitals reporting incidence in absolute data %(n/total)	
Range (n)	1-29*
Measured	29.2(7/24)*
Estimated	70.8(17/24)*
Reason for not answering % *(n/total)*	
Not measured	20.8 (5/24)
Reported as unknown in institute	29.2 (7/24)
Responder had no idea	25.0 (6/24)
No reason given for not responding	25.0(6/24)

***Data from (other) 24 hospitals were not comparable**

In general the CIN incidence was estimated in 28 hospitals, while measured in 15 hospitals.

When the question was not answered responders commented that this was not measured in their institute (20.8%; 5/24), or that this was unknown (29.2%, 7/24) or the responder acknowledged that he or she had no idea (25%, 6/24). The other six (25%, 6/24) hospitals gave no reason as why they were not able to answer the question (*table 6*).

DISCUSSION

Our study shows that all hospitals in the Netherlands use a CIN prevention guideline, consisting of the VMS guideline and/or the CBO guideline. The majority of Dutch hospitals (70.1%) have applied a CIN prevention strategy based on the VMS guideline, implying that renal function is determined in every patient who is exposed to intravascular iodinated contrast medium.

The execution of these guidelines has proven to be cumbersome. Almost 50% of the hospitals experienced problems with the compliance to the guideline in their institution. When we looked at the general (measures for all patients) and specific measures (measures in high-risk patients) there seemed to be fewer problems in hospitals using the CBO guideline than the VMS guideline. Our results show a great variation in the practical implementation of the guideline, concerning

the responsibility, timing and the way renal function was determined. Several hospitals have a specialised outpatient clinic to manage patients undergoing intravascular iodinated contrast enhanced procedures, mostly established to coordinate and execute the special measures in patients at risk. Nearly one third of the hospitals did not determine renal function after intravascular iodinated contrast medium administration. It was only in hospitals with a specialised outpatient clinic that all high-risk patients had a consistent follow-up procedure. When we asked about CIN incidence it was remarkable that the large majority of hospitals did not know the exact incidence in their hospital. Because data were obtained from different groups of patients with different risk profiles and were not always reported as percentages, available data could not be considered comparable.

The above-mentioned problems and differences are well known when it comes to the compliance of guidelines in general.[28] This could be related to the laborious process, especially in the follow-up of patients at risk. The inconsistencies and variation might also to some extent be fuelled by the lack of evidence for the prevention measures for intravenous contrast medium administration which concerns the bulk of the examinations with intravascular contrast medium administration.[23,24,28-30] The effectiveness of the proposed CIN prevention strategy has not been proven in a randomised controlled manner, neither has the special measure of prophylactic intravenous hydration before and after intravascular iodinated contrast medium exposure.[23,24,28,29,31] The absence of CIN registration (in most institutes) underscores this. Because the lack of (uniform) registration before and after the implementation of the guidelines, we do not know if the CIN incidence (in the Netherlands) has diminished as result of the implementation.

Our study has some limitations. Our outcomes are based on a questionnaire instead of patient data collected in a prospective manner. To increase the response, we limited the number of questions, which makes the inventory less detailed. However, responders often used the option to include free comments but it is not known whether the points raised would also be applicable to other departments and institutions. We only asked radiologists to fill in the questionnaire, thus we cannot be certain that the information provided can be generalised for other departments in the same institution where intravascular iodinated contrast media are used (e.g. cardiology department). However, most iodinated intravascular contrast administration takes place in the radiology department. Thereby, it is unpractical to have two different CIN prevention programs in place in an institution as the execution of the guideline involves many departments.[30] Furthermore, not all Dutch hospitals participated in this survey, although the response was substantial (74.4%) and therefore the results are most likely a good reflection of all Dutch hospitals. Selection bias with respect to the use of a CIN prevention guideline was minimised by completing the information by phone and internet. This does not have to reflect the compliance or adherence in these hospitals; therefore, for these data a selection bias might be more prominent.

Based on the inventory of the current practice of CIN prevention in the Netherlands, it may be concluded that most Dutch hospitals use a prevention guideline. There was considerable variation in the execution of the guidelines and there were substantial compliance problems. The experienced problems were similar between the two guidelines.

The follow-up procedure in specialised outpatient clinics was more consistent.

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APPENDIX

Questionnaire: Prevention programme/ guideline contrast-induced nephropathy

Q1: Radiologist since .....(e.g. 2001)

Q2: Name of hospital where you are currently working?

.....

Q3: Selection of high-risk patient according to which of the following guidelines?

◯ VMS guideline
◯ CBO guideline
◯ Other.....

Q4: Formula used for determination of renal function (eGFR)?
◯ MDRD-4 point formula (serum creatinine, age, gender, African European)
◯ MDRD-6 point formula (serum creatinine, urea, albumin, age, gender, African American)
◯ Cockroft-Gault (age, weight, serum creatinine)
◯ Other.....

Q5: Same selection procedure for inpatients and outpatients?

◯ Yes
◯ No

Q6: In normal (low-risk) patients and high-risk patients certain general measures need to be taken, e.g. stopping of diuretics, non-steroid inflammatory drugs if possible 24 hours prior to examination. Who is responsible for conducting the general measures?

◯ Nuclear/ Radiology department
◯ Requesting physician
◯ Outpatient clinic (specialised in preventing CIN)
◯ Other.....

Q7: In patients identified as being at risk, specific measures need to be taken, e.g. stopping metformin, intravenous hydration and verification of eGFR. Who is responsible for conducting the specific measures?

◯ Nuclear/ Radiology department
◯ Requesting physician
◯ Outpatient clinic (specialised in preventing CIN)
◯ Other.....

Q8: One of the guidelines aspects is the verification of renal function until normal (pre-contrast administration) values are reached. Is this verified? If so when?

◯ eGFR is not determined
◯ >2 days
◯ Between 2-3 days
◯ Between 3-5 days
◯ Between 5-7 days
◯ Other.....

Q9: Do problems concerning the logistics/ execution of the identification of patients at risk occur?

◯ Yes
◯ No

Q10: Do problems concerning the logistics/ implementation of the general and specific measures occur?

◯ Yes
◯ No