European Journal of Radiology 82 (2013) e387–e399

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Contrast induced nephropathy in patients undergoing intravenous (IV) contrast enhanced computed tomography (CECT) and the relationship with risk factors: A meta-analysis

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ARTICLE INFO

Article history:
Received 7 February 2013
Received in revised form 4 April 2013
Accepted 24 April 2013

Keywords:
Computed tomography
Contrast medium
Nephropathy
Prevention
Risk factors

ABSTRACT

Purpose: To summarize the incidence of contrast-induced nephropathy (CIN) and associations between CIN incidence and risk factors in patients undergoing intravenous contrast-enhanced computed tomography (CECT) with low- or iso-osmolar iodinated contrast medium.

Methods: This review is performed in accordance with the preferred reporting items in systematic reviews and meta-analysis (PRISMA) guidelines. We searched the MEDLINE, EMBASE and Cochrane databases from 2002 till November 2012. Two reviewers included papers and extracted data. The pooled data were analysed by either fixed or random-effects approach depending on heterogeneity defined as the I^2 index.

Results: 42 articles with 18,790 patients (mean age 61.5 years (range: 38–83 years)) were included. The mean baseline eGFR was 59.8 mL/min and ranged from 4 to 256 mL/min. Of all patients 45.0% had an estimated glomerular filtration rate (eGFR) < 60 mL/min, 55.2% had hypertension; 20.2% had diabetes mellitus (DM) and 6.5% had congestive heart failure (CHF).

The overall pooled CIN incidence, defined as a SCr increase of ≥25% or ≥0.5 mg/dL, was 4.96% (95%CI: 3.79–6.47). Data analysis showed associations between CIN and the presence of renal insufficiency, DM, malignancy, age > 65 years and use of non-steroidal anti-inflammatory drugs (NSAID's) with odds ratios of 1.73 (95%CI: 1.06–2.82), 1.87 (95%CI: 1.55–2.26), 1.79 (95%CI: 1.03–3.11), 1.95 (95%CI: 1.02–3.70) and 2.32 (95%CI: 1.04–5.19), respectively while hypertension, anaemia and CFH were not associated ($p = 0.13$, $p = 0.38$, $p = 0.40$).

Conclusion: The mean incidence of CIN after intravenous iodinated CECT was low and associated with renal insufficiency, diabetes, presence of malignancy, old age and NSAID's use.

1. Introduction

Contrast-induced nephropathy (CIN) is a major adverse effect of intravascular administration of iodinated contrast medium [1]. In most studies it is defined as an absolute (≥0.5 mg/dL) or relative (≥25%) increase in serum creatinine (SCr) within 48–72 h after iodinated contrast medium administration in absence of another explanation for the rise in SCr [1].

CIN has been associated with an increase in morbidity, mortality and medical resource consumption [2]. In an effort to reduce CIN, guidelines have been developed. Most (inter)national guidelines indicate that patients at risk should be identified by screening for the presence of risk factors in combination with renal insufficiency [3–6]. Usually this concerns verification of the estimated glomerular filtration rate (eGFR) or SCr and risk factors such as diabetes, hypertension and old age. If patients are at risk, preventive measures should be taken [3–6]. These guidelines have led to discussion, mostly about the identification of patients at risk and the type of prevention measures that usually are recommended by these guidelines [7–9].

One of the problems is that most of the evidence used to develop these guidelines is based on studies evaluating patients undergoing intra arterial cardiac interventions with high volume of sometimes high osmolar iodinated contrast media [9,10]. This population differs significantly from the patient population undergoing iodinated contrast enhanced computed tomography (CECT), as does the occurrence of adverse events [7]. This could be related to a difference in association with risk factors and the development of CIN [10,11].

A recently published systematic review showed a pooled incidence of CIN of 6.4% in patients undergoing intravenous CECT and higher incidences of CIN were seen in patients with renal

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http://dx.doi.org/10.1016/j.ejrad.2013.04.029

insufficiency or diabetes mellitus compared to patients without these risk factors [12]. No associations were seen between CIN incidence and hypertension or with the volume of administrated iodine.

However in most guidelines other risk factors are also mentioned, such as age, gender, race, anaemia, congestive heart diseases, use of nephrotoxic medication, dehydration, and cardiovascular diseases and these were not taken into account in the aforementioned meta analysis [3–6,12].

We hypothesize that the CIN incidence is lower in a population representing the large majority of patients referred for CECT, mostly outpatients who are hemodynamically and respiratory stable. Further it is important to identify whether risk factors mentioned in guidelines are associated with CIN incidence in patients receiving intravenous iodinated contrast medium. Up till now the results of clinical trials about the association between CIN and different risk factors as mentioned in most prevention guidelines, differ in outcome and very seldom mention more than three risk factors.

The purpose of our meta-analysis was to summarize the incidence of CIN in patients undergoing intravenous CECT and to study associations between CIN and several risk factors that are mentioned in most prevention guidelines.

2. Materials and methods

2.1. Search strategy and study selection

We searched the MEDLINE, EMBASE and Cochrane databases from 2002 till 10th of November 2012 to identify all relevant studies on CIN. In the previously mentioned meta-analysis of Kooiman et al., no papers published before 2002 were found to be relevant [12]. The systematic review was conducted in accordance with the Preferred Reporting Items in Systematic Reviews and Meta-analysis (PRISMA) guidelines [13].

We used the following search terms: (CIN (Title, Abstract, Keyword) AND Nephropathy (Title, Abstract, Keyword) OR Contrast-induced nephropathy (Title, Abstract, Keyword) OR Contrast induced nephropathy (Title, Abstract, Keyword)). The search strategy is described in detail in Appendix 1. Firstly all studies not related to CIN were excluded. Secondly all comments, reviews and conference papers were excluded to select potential relevant papers. Two reviewers checked all potential relevant data to select relevant papers. Of all relevant papers full text were retrieved for further checking of inclusion and exclusion criteria.

2.2. Inclusion and exclusion criteria

Inclusion and exclusion criteria were checked independently by two reviewers SM and SB and disagreements were resolved by consensus.

Papers were included when: (1) written in English, German, Dutch, French, Italian and Spanish; (2) patients underwent intravenous CECT (if data on intra-arterial examinations were also given and data could not be selected for only intravenous administration of contrast medium, the study was not included); (3) patients underwent intravenous CECT with low- or iso-osmolar contrast medium (if data on high osmolar medium was also given, and could not be split for low osmolar medium, the study was not included); (4) CIN incidence and risk factors were presented and (5) follow-up period for determining CIN between 24 h and 1 week after intravenous CECT (if follow-up was done >1 week and the follow-up data between 24 h and 1 weeks could not be selected, the study was not included).

The exclusion criteria were: (1) duplicate publication (most recent paper was included for analysis); (2) ICU patients included and these data could not be separately identified; (3) less than 10 patients with intravenous CECT.

Of all included articles, data on methodological assessment, baseline patient characteristics, preventive measures, characteristics of computed tomography (CT), CIN incidence determination were assessed by the same reviewers independently SM and SB. A third reviewer [bDV] checked all collected data and was the decisive factor in case of disagreement between the first two reviewers.

2.3. Methodological assessment

Methodological assessment of the included studies was done according to the Delphi list for randomized controlled trials (RCT) [14], combined with the signalling aspects of the QUADAS-2 tool for diagnostic accuracy studies [15]. The following characteristics were assessed whether: (1) the study was a cohort or RCT; (2) the study was a single centre or multicentre study; (3) data were extracted prospectively or retrospectively; (4) a consecutive or random sample of patients was enrolled; (5) inclusion/exclusion criteria were specified; (6) the spectrum of patients was representative of the patients who will receive the test in real life practice; (7) the administration of contrast medium was described in sufficient detail to permit its replication; (8) the time period between contrast medium administration and follow-up was reasonable (performed within 2–4 days, 48–92 h); (9) the whole (or random sample) underwent follow-up for occurrence/determination of CIN.

In case of a RCT, the following data were also assessed, whether: (10) the method of randomization was described; (11) groups were similar at baseline regarding the most important indicators; (12) relevant data presented with confidence intervals (CI) and (13) the RCT was double blinded.

2.4. Baseline patient characteristics

The following data were assessed: (1) number of patients included and analysed; (2) age of patients (mean ± SD, median and/or range); (3) proportion of patients >60 years and/or >75 years; (4) male: female ratio; (5) baseline eGFR (mean ± SD, median and/or range); (6) proportion of patients with an eGFR < 60 mL/min and proportion of patients with an eGFR < 45 mL/min [3,5]; (7) method for calculation eGFR (Cockcroft-Gault formula or Modification of Diet in Renal Disease (MDRD-4 or MDRD-6)) (because both formula's were used in the papers included in the meta-analysis the eGFR is expressed in mL/min throughout the article); (8) baseline SCr (mean ± SD, median and/or range); (9) proportion of patients with renal insufficiency: (10) proportion of patients with diabetes mellitus: (11) proportion of patients with hypertension; (12) proportion of patients using nephrotoxic medication; (13) proportion of patients with anaemia; (14) proportion of patients with congestive heart disease and (15) proportion of patients with cardiovascular diseases. In case data on other risks factors, such as liver disease or stroke were presented, the proportions of patients with these conditions were also extracted.

If data on proportion of patients with renal insufficiency or diabetes mellitus were not complete, we contacted the corresponding authors of these papers for additional data.

2.5. Preventive measures

We also recorded whether prevention measures, before or after the CT examination, were performed. If this was done, details on the program were assessed and also the proportion of patients who received prevention measures (e.g. hydration and discontinuation of nephrotoxic medication).