Maastricht Investigation of Renal function in Absence of- and post-Contrast in patients with estimated glomerular filtration rate LEss than 30mL/min/1.73m2 (MIRACLE)

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Renal disorders (excl nephropathies)
Study type	Observational invasive

Summary

ID

NL-OMON54949

Source
ToetsingOnline

Brief title
MIRACLE

Condition

- Renal disorders (excl nephropathies)

Synonym
post-contrast acute kidney injury; post-contrast acute increase in serum creatinine

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: acute kidney injury, intravascular iodinated contrast material administration

Outcome measures

Primary outcome

In the context of post-contrast acute kidney injury, change in serum creatinine is the gold standard recommended in all (inter)national guidelines on safe use of iodinated contrast material. The primary outcome of the current study is peak changes in serum creatinine within 5 days from a baseline measurement, determined within prespecified periods (see Section J, Table 1). The effect of contrast administration will be expressed as the mean intra-patient difference in peak changes in serum creatinine between 5-day pre- and post-contrast periods.

Secondary outcome

Other outcomes are peak changes in serum creatinine occurring at 1 month post-contrast compared to those occurring in absence of contrast; time to post-contrast peak change in serum creatinine; incidences of classic and KDIGO definitions of acute kidney injury in absence of contrast compared to post-contrast; changes in eGFR within 5 days from baseline in absence of and post-contrast; change in eGFR at 1-month post-contrast; incidences of eGFR decline >=5 mL/min/1.73m2, dialysis and mortality at 1-month post-contrast; and time to naturally excreted contrast-free urine. Finally, samples will be stored

in order to determine serum contrast (patients with retention or <100% excretion of contrast in urine) and/or serum/urine renal damage markers (such as KIM-1, NGAL and IL-18).

The following definitions for acute kidney injury will be used, based on baseline serum creatinine values (visits 1.0 and 2.0) and peak serum creatinine changes from baseline (visits 1.1-1.5 and 2.1-2.5; see Section J, Table 1):
- an increase in serum creatinine greater than 44**mol/l or 25% from baseline (classic)
- an increase in serum creatinine greater than 26.5 *mol/L from baseline or more than 1.5 times the baseline value (KDIGO)

8.1.3 Other study parameters/endpoints

Relevant baseline characteristics of patients will be reported to enable a detailed description of the study population. To enable subgroup analyses, data will be collected on 1) prophylactic hydration (yes vs no); 2) administration route (intra-arterial versus intravenous contrast administration); 3) contrast volume (high vs low) and 4) comorbidity (presence vs absence of diabetes).

Study description

Background summary

Intravascular iodinated contrast administration has become crucial to modern medicine. Currently it is estimated that over 250 million injections are given each year worldwide during medical scans and interventions.1 For over 50 years now, acute kidney injury caused by intravascular administration of iodinated

contrast material has been considered a leading cause of hospital-acquired renal failure.2 As a result, contrast has been withheld in fear of kidney injury leading to misdiagnoses and delayed appropriate patient management.

An acute predefined increase in serum creatinine is considered an indicator of acute kidney injury (AKI).KDIGO, NVvR When such an acute increase in serum creatinine occurs within 2-5 days post-contrast in absence of another aetiology, it is assumed to be iodinated contrast administration induced acute kidney injury. However, careful review of the enormous amount of existing literature on the subject leads to the conclusion that risks of post-contrast acute kidney injury and clinical consequences thereof have been grossly overestimated. Reasons for this may be manifold. A bias exists in literature toward studies in cardiac angiography, where both inherent population and procedural risk factors abound and confuse the issue.3 Furthermore, all prospective studies published in literature lack control groups not receiving iodinated contrast material.4 Serum creatinine, changes in which are used to determine the presence or absence of acute kidney injury, is a non-specific surrogate and imperfect marker for renal function.5 It is influenced by factors such as muscle mass, diet, hydration, activity, blood pressure, and (changes in) medication, it shows diurnal and seasonal fluctuations, and is often unstable in patients with health issues.6,7 Without control groups, rises in creatinine are attributed to contrast administration without considering normal creatinine fluctuations or other causes. The implications of the often transient and acute rise in serum creatinine that represents PC-AKI are also unclear, and it is unsure whether longer-term negative outcomes are inherent to the population studied or a result of contrast administration. Several studies have shown correlations between PC-AKI and increased morbidity and mortality risk, but whether PC-AKI is a marker or part of a causative process is not known.8-12 There are several studies that have attempted to evaluate the causal relationship between contrast exposure and nephrotoxicity.13-15 However, most of these are observational and retrospective in nature. Serum creatinine increase indicating acute kidney injury has been shown to occur in absence of iodinated contrast, and incidences are sufficient to eclipse those of post-contrast acute kidney injury (PC-AKI).14,15 In other words, measuring post-contrast change in serum creatinine yields mostly noise, with only a few instances of acute kidney injury. The issue with retrospective studies is that they often cannot control for confounders and therefore cannot give us causation, only association. Furthermore, selection bias plays a role, since only patients with repeated renal function measurements can be included in such studies. No prospective studies on incidences of AKI in absence of contrast have been done.

Another reason for overestimation of the risk for renal function is that the basis of PC-AKI has been laid in another era of contrast material administration. Many advances have been implemented since PC-AKI and associated long-term risk were first reported.16 Not only have contrast media greatly evolved - from toxic cell-invading salts, through high-osmolality ionic, an

finally to non-ionic low-osmolality structures -,17 injection protocol parameters have also been the subject of many optimisation studies.18-30 Reductions in contrast volumes of up to 75% have been achieved using relatively low-iodine concentration contrast agents whilst maintaining sufficient diagnostic image quality. In other words, we currently operate in a new, safer era of iodinated contrast administration.31 Contrast toxicity in clinical practice can be expected to likewise have changed.

Guidelines on the use of intravascular iodinated contrast material the world over have changed in accordance with the above insights. Whereas intravascular iodinated contrast was thought to pose a risk for renal function of all patients in the past, the high risk group has been adjusted to include ever smaller subgroups of patients with chronic kidney disease (i.e., eGFR <60 ml/min/1.73m2).32-33 Since 2018 it is widely accepted that patients with eGFR <30 mL/min/1.73m2 are most at risk of renal injury after intravascular iodinated contrast material injection.34-38 This consensus is not based on available data, since data on eGFR <30 ml/min/1.73m2 patients is rare in literature.39-40

Studies to date have not been able to distinguish acute kidney injury caused by iodinated contrast administration from that for which no causal link is established, and the question at this time is whether iodinated contrast administration (still) induces renal damage in the current clinical setting in patients with eGFR <30 mL/min/1.73m2. This would best be answered by randomised controlled trials comparing eGFR <30 mL/min/1.73m2 patients receiving iodinated contrast versus a placebo injection. However, such trials are unlikely given evident ethical issues.

The current controlled prospective observational study proposes a solution to the above dilemma: intra-patient comparisons of peak changes in renal function (serum creatinine) in absence of- and post- intravascular iodinated contrast administration, to elucidate the relationship between renal function and contrast administration in elective patients with eGFR <30 mL/min/1.73m2. Risk of short-term dialysis and mortality will also be evaluated.

Study objective

The current prospective observational study proposes to use intra-patient comparisons of periods without and with contrast to elucidate the relationship between renal function and contrast administration in this population. The central question is: is there a difference between peak change in serum creatinine within 5 days in absence of- and post-contrast?

Primary objective:
The primary aim is to evaluate the effect of intravascular iodinated contrast administration on renal function as represented by changes in serum creatinine, in patients with eGFR <30 mL/min/1.73m2.

Secondary objectives:
Secondary aims are to determine the following in patients with eGFR <30 mL/min/1.73m2: time to post-contrast peak change in serum creatinine; incidences of classic and KDIGO definitions of acute kidney injury in absence of contrast compared to post-contrast; changes in eGFR within 5 days from baseline in absence of and post-contrast. In addition, effects up to 1-month post-contrast will be evaluated through change in eGFR, incidences of eGFR decline >=5 mL/min/1.73m2, and incidences of dialysis and mortality. A final aim is to determine urine elimination time of intravascular iodinated contrast in patients with eGFR <30 mL/min/1.73m2.

To evaluate whether the effect of contrast administration on renal function is modified by specific situations, exploratory subgroup analyses will be prespecified (see section 3).

Study design

MIRACLE is a single centre study at Maastricht UMC+, amongst patients referred for an elective procedure with intravascular iodinated contrast and with an eGFR <30 mL/min/1.73m2.

The study design is a prospective observational study using intra-patient comparisons, so that each patient functions as his/her own control (see Section J, Table 1).

In order to determine the effect of intravascular iodinated contrast administration on renal function, most guidelines on safe use of contrast material recommend measuring post-contrast serum creatinine within 2-3 days (the Dutch guideline recommends measuring serum creatinine within 2-7 days, presumably for logistic reasons). However, although serum creatinine rises within 48 h, it has been shown to peak between 4- and 5-days post-contrast on average.30 Therefore, in this study, peak changes in serum creatinine within 5 days will be determined. This will be done before (= in absence of contrast), after (=post-contrast), and at 1-month post contrast (=1-month post contrast in absence of contrast).

In addition, peak changes in eGFR, 1-month change in eGFR and incidences of dialysis and mortality will be recorded. Patients will also be asked to collect urine every time they naturally urinate and to note time and date on the container provided. Urine will be collected during approximately 4 days: from first urination after intravascular iodinated contrast administration until the time of visit 2.5 (see Section J, Table 1). Both urine and serum samples will be stored at the biobank Maastricht UMC+ for renal function/renal damage marker assays.

The study will include 72 patients. Each patient will be followed for the duration of approximately 40 days.

Exploratory subgroup analyses will be performed to evaluate whether specific situations result in higher vulnerability of patients to an increase in peak change after contrast administration (when compared with the peak change before contrast administration). Patients will be categorized into two subgroups according to the following pre-defined factors:

1. Intravenous prophylactic hydration (yes vs no),
2. Administration route (intra-arterial versus intravenous contrast administration)
3. Volume of contrast (high versus low)
4. Co-morbidity (presence vs absence of diabetes)

To find out whether there is effect modification (interaction), it will be explored whether the magnitude of the mean difference in peak change in serum creatinine before and after contrast administration varies between subgroups.

Study burden and risks

Table 1 (see Section J) gives a representation of data collection and the burden of participating in this study. Patients will follow standard care. Participation in this study entails 11 days of study contact, followed by 25 days without, then another 6 days of study contact. The intake visit should take less than 30 minutes, all other study visits are expected to last no longer than 10 minutes. No filling in of questionnaires is required. Baseline characteristics and medication may be orally checked with the patient during all three baseline and the final visits. Adverse events will be asked after at each visit. Inasmuch as possible, or inasmuch the patient wishes, follow-up venepunctures will be done at home.

In routine care renal function of patients with eGFR <30 mL/min/1.73m2 is monitored relatively frequently, and two blood samples - before and once within 2-5 days after any intravascular iodinated contrast material administration - are standard care at Maastricht UMC+. Sometimes another two blood samples are also standard care: at the time of referral and at 1-month post-contrast. In total thirteen to fifteen extra venepuncture blood samples will be taken for this study over the course of approximately 40 days (see Section J, Table 1); never more than one in one day and not more than 10 mL at a time. The risks of venepuncture and participation in this study are deemed negligible.

Longer elimination time of contrast will potentially increase renal toxicity. In order to determine elimination time and identify which patients retain contrast, patients will be asked to collect urine every time they naturally urinate and to note time and date on the container provided. Urine will be collected for approximately 4 days: from first urination after intravascular iodinated contrast administration until the study visit on day 5 post-contrast (visit 2.5; see Section J, Table 1). Containers will be collected during visits.

Benefits:
Patients are not expected to personally benefit from participating in this study, although their renal function will be monitored extra closely. Patients with eGFR <30 mL/min/1.73m2 are most at risk of renal injury after intravascular iodinated contrast material injection. Whereas such contrast administration appears to be safe for the majority of patients even amongst those with eGFR <30 mL/min/1.73m2, reports of individuals with post-contrast adverse events persist. On the other hand, contrast has been withheld in fear of kidney injury with misdiagnoses and delayed appropriate patient management as a result. Results of this study may help better determine the causal relationship between contrast exposure and nephrotoxicity, identify which individual patients are at risk, and help to better determine safety of intravascular iodinated contrast administration in future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with eGFR <30 mL/min/1.73m2 in absence of dialysis referred for an elective procedure with intravascular administration of iodinated contrast material at Maastricht UMC+

Exclusion criteria

age <18 years; dialysis or pre-dialysis; intravascular contrast administration within 30 days before the first baseline; emergency or intensive care status; inability to complete the follow-up.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	72
Type:	Anticipated

Ethics review

Approved WMO

Date:	05-05-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	ClinicalTrials.gov NCT04598516
CCMO	NL74947.068.20