A Maastricht Contrast-Induiced-Nehropathy Guideline study (AMACING): prevention guidelines - appropriate and cost effective?

Published: 14-05-2014
Last updated: 20-04-2024

The AMACING study aims to evaluate the (cost) effectiveness of guideline prescribed intravenous prophylactic hydration in the prevention of: CIN, decrease in renal function, renal damage, 30-day morbidity and 30-day mortality; taking into account...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON44751

Source
ToetsingOnline

Brief title
AMACING study

Condition

- Nephropathies

Synonym
acute kidney injury (AKI), acute renal insufficiency

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 (AKI), contrast induced nephropathy (CIN), prophylactic intravenous hydration

Outcome measures

Primary outcome

The aim of the guidelines is to prevent CIN. Therefore, even though clinically relevant outcomes would be a preferable outcome measure, an evaluation of the (cost) effectiveness of the prophylactic treatment prescribed by these guidelines must have CIN incidence as primary outcome measure.

The costs per CIN case prevented will be calculated based on the absolute difference in CIN incidence between the randomized groups with and without prophylactic intravenous hydration (non-inferiority randomized trial).

In addition, we will evaluate the performance of prophylactic intravenous hydration in the prevention of the clinically relevant effects: decrease in renal function, renal damage and 30-day morbidity/mortality. In the evaluation, we shall take complications of prophylactic intravenous hydration into account.

Secondary outcome

I. Biological variation of creatinine & CIN incidence

Difference in CIN incidence using guideline-prescribed baseline values of serum creatinine (which may be up to 12 months old), and using true baseline serum creatinine values (measured on the day of contrast material administration and before start of the treatment)

II. Prophylactic hydration: Protection or dilution effect on serum creatinine

Serum creatinine changes during prophylactic hydration (dilution).

Kidney function and damage during the course of the treatment (using various biomarkers).

III. Prophylactic hydration: hydration status

Relationship between hydration status of patients (baseline and post-treatment) and CIN incidence, renal function, renal damage, adverse events, and 30-day morbidity/mortality.

IV. Cholesterol embolism

Serum and urine lactate-dehydrogenase (LDH) values, eosinophilia and eosinophiluria in patients with and without CIN.

V. Dose response

Dose-response curves between iodinated contrast material load (iodine load) and CIN, renal function, renal damage, adverse events, 30-day morbidity and mortality.

VI. 1-year dialysis and mortality incidences in the two RCT arms.

Subgroup analyses will be carried out on all levels (according to stratifications used).

Questionnaire-based data concerning treatment rating, generic quality of life (EQ-5D), costs, medicinal and health changes over a period of 30 days after the

contrast procedure will be recorded.

Evaluation of the effect of blood sample collection on laboratory outcomes:

Differences in the AMACING study laboratory outcomes obtained from

intraarterial, intravenous and capillary blood samples of a subgroup of our

patient population.

Study description

Background summary

Contrast-induced nephropathy (CIN) is a side-effect of intravascular administration of iodinated contrast material. It is defined as an absolute (>44*mol/l) or relative (>25%) increase in serum creatinine from baseline values within 48-72 hours of iodinated contrast material administration, and usually resolves within two weeks. In some cases CIN has been associated with persistent renal failure, increased risk of dialysis, and mortality. It is not clear however, whether CIN is causally related to this increased risk or whether risk of morbidity and mortality is inherent in those at risk of CIN.

CIN itself is asymptomatic and no treatment for CIN exists. Therefore, the focus lies on its prevention. Prevention guidelines have been drawn up in most countries and been implemented in most radiological departments. In the Netherlands, currently two guidelines for the prevention of CIN co-exist, issued by CBO (Centraal BegeleidingsOrgaan) and VMS (Veiligheids Management Systeem).

The prevention guidelines aim to increase patient safety by identifying patients that may be at risk of CIN (mostly patients with chronic renal insufficiency), and subsequently administering prophylactic intravenous hydration to the so identified patients, in order to prevent CIN (intravenous normal saline 4-12 hours before and 4-12 hours after exposure to iodinated contrast material).

Needless to say, the introduction of these guidelines has had a great impact on patient- and health care burden. In the Netherlands alone it is estimated that yearly 100 000 to 150 000 patients receive the prophylactic treatment, incurring a total cost of over 50 million Euro. Considering the steady yearly increase of contrast procedures and the ageing population, it is evident that,

in future, these numbers shall only further increase.

The prophylactic treatment prescribed by the guidelines is based on a consensus of the opinion of experts in general agreement that the treatment is beneficial. However, and perhaps surprisingly, the effectiveness of prophylactic hydration has never been adequately evaluated. Randomised double-blinded trials comparing prophylactic intravenous hydration with a proper control group receiving no prophylactic treatment are not available, and baseline CIN incidences in untreated populations are unknown. Thus, it is not clear whether prophylactic hydration achieves its aim to prevent CIN.

Furthermore, studies evaluating the effect of various prophylactic treatments invariably focus on CIN instead of clinically relevant measures as primary outcome. CIN itself being asymptomatic, it is important to determine whether prophylactic treatment has a preventive effect on clinically relevant endpoints sometimes associated with CIN, such as dialysis and mortality. Consider for example: even if it transpires that prophylactic treatment reduces CIN incidence, it may be that intravenous hydration merely dilutes serum creatinine to such an extent that it masks CIN, having no protective effect on renal function. It has been shown that changes in volume status can influence serum creatinine levels, but a potential dilution effect of intravenous hydration has not been investigated to date.

On the other hand, it is important to realise that prophylactic intravenous hydration is not without risk. Patients may suffer mild to serious complications ranging from phlebitis to pulmonary oedema, the latter being potentially fatal. Those patients selected according to the guidelines for the risk of CIN - risk factors including poor renal function, age, diabetes and cardiac disease - are especially sensitive to complications of intravenous hydration. The risk of intravenous hydration in this population has not as yet been charted, and is not taken into account by guidelines for the prevention of CIN.

It stands to reason that a patient*s pre-existing hydration status may be a determining factor for the net effect of intravenous hydration: from the same treatment dehydrated patients may enjoy benefits, whereas overhydrated patients may suffer complications. The importance of hydration status in determining the effects of prophylactic hydration, however, has not been investigated to date.

The mechanism by which prophylactic hydration may protect renal function from injury by iodinated contrast material is unclear, as the mechanism by which iodinated contrast material may induce CIN is unclear. Indeed, in patients with chronic renal insufficiency biological variation of serum creatinine in the absence of contrast material has been shown to be indistinguishable from CIN. The question has arisen in recent literature whether CIN is anything more than an asymptomatic increase in serum creatinine, lacking any prognostic negative impact, and not significantly different from that observed in controls not

receiving iodinated contrast material.
Recent studies comparing patients with chronic renal deficiency receiving intravascular iodinated contrast material to those patients not receiving iodinated contrast material found no association between increase in serum creatinine (CIN) and contrast administration. Indeed, it has been suggested that renal damage after intra-arterial procedures is caused, not by contrast material, but by cholesterol embolism arising from the erosion of aortic atheromatous plaques by the catheter used in such procedures.

It is perhaps of importance to note that relatively recently, monomeric non-ionic low-osmolar iodinated contrast materials - with less toxic properties than *traditional* contrast materials - have been introduced and are now widely used, perhaps altering the landscape of CIN.

In order to be able to take effective measures to the benefit of patient safety, it is important to distinguish between the mechanisms underlying CIN and the ensuing increased risk of morbidity and mortality: whether it be biological variation of serum creatinine, renal damage, or cholesterol embolism; whether any causality exists between these and iodinated contrast material; and whether prophylactic intravenous hydration can prevent these from occurring without incurring more risks than it removes. These, in short, are the aims of the AMACING study.

Evaluation of the effect of blood sample collection on laboratory outcomes:
The AMACING study aims to minimise poatoent burden, and consequently blood is not always collected in the same manner. It is known that certain laboratory results differ in blood drawn intra-arterially, intravenously or from capillaries, however it is not known whether this is so for (all) laboratory results obtained for the AMCING study. In order to further enhance correct interpretation of our results it is important to assess which, if any differeneces exist and whether these differences are predictable.

Study objective

The AMACING study aims to evaluate the (cost) effectiveness of guideline prescribed intravenous prophylactic hydration in the prevention of: CIN, decrease in renal function, renal damage, 30-day morbidity and 30-day mortality; taking into account complications of intravenous hydration.

In addition, we shall attempt to answer the following questions:
I. Does biological and/or seasonal serum creatinine variation influence CIN incidence recorded in clinical practice?
II. Does intravenous hydration protect renal function and prevent renal damage, or does it merely dilute serum creatinine, masking the rise that would otherwise be diagnosed as CIN?
III. Is intravenous hydration beneficial in all patients or only in those that

have a reduced circulating volume (are dehydrated) at the time of iodinated contrast material administration?
IV. Does cholesterol embolization contribute to CIN?
V. Does a dose-response relationship exist between iodinated contrast material administration and CIN, renal function, renal damage and 30-day morbidity and mortality

Evaluation of the effect of blood sample collection on laboratory outcomes:
Do AMACING study laboratory outcomes differ when obtained from intraarterial (from the access already available for catheterisation), intravenous (via venapuncture) and capillary (fingerprick) blood samples?

Study design

Prospective non-inferiority randomized controlled trial comparing prophylactic intravenous hydration with normal saline according to current guidelines, to a control group not receiving intravenous hydration. Patients will be randomised using stratifications for different subgroups.

Intervention

Rather than an intervention, this study concerns the withholding of prophylactic treatment.
Patients identified according to current CBO guidelines as being at risk of CIN and having been referred for prophylactic treatment will be randomised to either receive:
1. Standard care prophylactic treatment * i.e. intravenous hydration with normal saline (0.9% NaCl) 4-12 hours before and 4-12 hours after administration of iodinated contrast material.
2. No prophylactic intravenous hydration.

Study burden and risks

Patient Burden
Beyond the requirements of standard care, patient burden when participating in AMACING will be as follows:
- Blood samples
2-3 blood samples of 17.5ml each will be collected on the day of the contrast procedure for which no extra venepunctures are required since blood samples can be taken from the pre-installed access device, installed for either iodinated contrast material administration or for the prophylactic intravenous hydration (2 samples will be collected from patients not receiving intravenous hydration i.e. pre- and post- contrast procedure; 3 samples will be collected from patients receiving intravenous hydration i.e. before the start of the treatment, after pre-hydration and after post-hydration);
In order to evaluate whether differences in blood collection methods (a.o.

different access points) influence laboratory results, we will ask a subgroup of patients * patients that will receive intra-arterial contrast via femoral entry * for one extra 10 to 20 ml of blood withdrawal: a few drops from finger prick and the rest by venepuncture. We will ask this BEFORE informed consent is given for participation in the AMACING study.
In addition, a 17.5ml blood sample will be collected at the 3 follow-up time-points of 2-5, 10-14 and 28-32 days after the contrast procedure.
- Urine samples
2-3 urine samples will be collected on the day of the contrast procedure (2 from patients not receiving intravenous hydration: pre- and post- contrast procedure; 3 from patients receiving intravenous hydration: before the start of the treatment, after pre-hydration and after post-hydration). The first sample can be taken in from home.
In addition, urine samples will be collected at the 3 follow-up time-points of 2-5, 10-14 and 28-32 days after the contrast procedure (these can be taken in from home).
- Physical measurements
We shall measure the patients* length once at baseline.
Blood pressure, pulse, bio impedance and weight will be measured at all time-points
(i.e. before the contrast procedure /pre-hydration, after pre-hydration, after contrast procedure /post-hydration, and at 2-5, 10-14, and 28-32 days after the contrast procedure).
- Questionnaires
Patients will be asked to fill in a questionnaire before and after the (treatment surrounding the) contrast procedure, and at each follow-up time-point. The filling in of these questionnaires should not take more than approximately 15 minutes each time.

Blood and urine samples will be stored at the MUMC Biobank for a maximum of 10 years.

Patients will be asked to make extra visits to the outpatient clinic for this trial. The visit and a 5ml blood sample at 2-5 days after the contrast procedure is standard care for our patient group (i.e. patients considered to be at risk of CIN according to the guidelines), as is the follow up visit at 10-14 days for those patients whose renal function deviates from baseline at 2-5 days, and the follow up visit at 28-32 days for those patients whose renal function deviates from baseline at 10-14 days.

Patient risk
Any risk incurred by participating in the aMACING study will be due to not receiving prophylactic intravenous hydration, since the collection of extra blood and urine samples incurs no extra risk. The true risk incurred from foregoing prophylactic treatment is unknown; however, recent literature suggests that it is likely to be minimal.

As stated above, the estimation of risk of CIN according to current guidelines is largely based on renal function and an eGFR threshold of <60 ml/min/1.73 m2 in combination with other risk factors is currently applied for prophylactic hydration according to Dutch guidelines. The incidence of chronic kidney disease stage 3 (eGFR 30-60 ml/min/1,73m2) in the Netherlands is 5.3%, of which at most an estimated third will have an eGFR <45 ml/min/1,73m2.

The European Society of Urogenital Radiology updated their CIN prevention guidelines in 2011 to indicate that intravenous prophylactic hydration is unnecessary in patients with an eGFR *45 ml/min/1.73m2 before intravenous contrast administration. Risk analyses revealed that intravenous contrast administration does not impose a nephrotoxic risk above an eGFR of 30ml/min/1.73m2. Indeed, zero incidence of dialysis and mortality is consistently reported after intravenous contrast administration, even in patients with severe renal insufficiency (eGFR<30) and in absence of prophylactic treatment. Since intravenous contrast administration procedures make up more than an estimated 70% of all contrast procedures this implies that prophylactic intravenous hydration is superfluous in the majority of patients currently receiving it. This patient population is also the larger proportion of patients to be included in our randomized controlled trial - an estimated 75% - who are therefore not thought to incur any risk from participation and not receiving prophylactic intravenous hydration.

The other 25% of patients we shall include may incur some risk of CIN: some have an eGFR between 30-44 ml/min/1.73m2, and some will be administered iodinated contrast material intra-arterially. The risk of CIN for the first group does not appear to be much elevated. A pooled overview of studies involving iodinated contrast material administration without prophylactic intravenous hydration yielded a CIN incidence of 3.9% (30/760): 25 of the 30 patients diagnosed with CIN had an eGFR of *45 ml/min/1.73 m2, and the baseline eGFR range of the other five CIN cases was not published.

As for the second group, although cases of long term adverse effects such as dialysis and mortality have rarely been reported following CIN after intravenous contrast administration, they have been reported after intra-arterial contrast administration. It has been thought, therefore, that intra-arterial administration led to more nefarious effects of iodinated contrast material than intravenous administration. This too, however, has been repeatedly put to question. A recent study found no difference in the risk of CIN after intra-arterial or intravenous contrast administration when an adjustment was made for patient related risk factors. Several studies found no increased risk of CIN after intra-arterial contrast administration as compared to intravenous administration, and one report even goes against all previous literature portraying a higher risk of morbidity and mortality after intravenous contrast administration than after intra-arterial administration. In short, it is not clear whether an increased risk of dialysis and mortality arises from contrast administration and CIN or whether it is inherent in the

patient population studied (i.e. a population requiring intra-arterial contrast procedures or requiring prophylactic hydration according to CIN prevention guidelines may conceivably have such an increased inherent risk). Indeed, chronic kidney disease, the main criterion in the guidelines for increased risk of CIN, in itself increases the risk of all-cause mortality, cardiovascular disease and progression to kidney failure.

Causality between an increase in serum creatinine after contrast administration (CIN) and adverse events has not been shown to exist. A recent meta-analysis by McDonald et al including a 157 140 contrast procedures showed no difference in incidences of CIN, dialysis, or death between patient groups receiving contrast material versus patients not receiving contrast material (7.2% CIN after contrast-enhanced scans versus 11.1% CIN after unenhanced scans in medium- to high-risk populations, suggesting that contrast material may not be causally related to CIN). More and more the opinion rises that, where it occurs, it is the risk inherent to specific populations that leads to higher morbidity/mortality incidence after CIN or specific administration routes, and that CIN is merely a marker for such populations instead of there being a causal relationship between CIN and morbidity/mortality, or even a causal relationship between all diagnosed CIN and intravascular contrast material administration.

On the other hand there is no evidence that prophylactic intravenous hydration has a protective effect on renal function. Almost all studies evaluating prophylactic intravenous hydration to date are uncontrolled trials or retrospective cohort analyses, often involving experimental additions to the standard administration of saline prescribed in the guidelines, and thus no conclusions on its effectiveness can be drawn.

In a recent Dutch study on CIN, 35 of 454 patients at risk of CIN according to current guidelines did not receive prophylactic intravenous hydration (for reasons unexplained); yet the incidence of CIN in this subgroup was not significantly higher than that found in the population having received prophylactic treatment (1/35 or 2.9%, versus 10/419 or 2.4%). Furthermore, in studies including patients receiving contrast material without prophylactic intravenous hydration (up to 94% of the patients did not undergo prophylactic intravenous hydration in some of these studies), and having severely diminished renal function (up to 49.3% of patients), low CIN incidences were seen (range: 1.3% - 5.2%; pooled incidence 3.6%), and zero long term adverse effects were reported.

Another issue is that prophylactic intravenous hydration is not without risk. Complications may occur, especially in those patients with cardiac and/or kidney disease, such as pulmonary oedema and/or cardiac failure which could lead to respiratory insufficiency. There is a considerable overlap between patients considered to be at risk of developing CIN and patients with at risk of complications from prophylactic intravenous hydration, and therefore this is

a real concern in clinical practice. A study performed in a Dutch hospital using Dutch CIN prevention guidelines reported an incidence of serious complications of intravenous hydration of 1.4% in hydrated patients. The incidence of clinically relevant events after CIN is <1% when monomeric non-ionic low-osmolar iodinated contrast material is used, thus putting the appropriateness of the prophylactic treatment to question, and highlighting the importance of its evaluation against a proper control group not receiving intravenous hydration.

The AMACING study will be pivotal in deciding the future role of prophylactic intravenous hydration in routine clinical practice. Considering the potential benefits of the results of this study to a large population - who are perhaps burdened with unnecessary and sometimes harmful treatments - and the potential benefits to our health care system in terms of efficiency and costs, we believe the risk for all patients included in this RCT is acceptable. The incidence of CIN is low, CIN itself has no direct relevant clinical implications, and prophylactic intravenous hydration may have negative effects largely disregarded until now. Based on current evidence, therefore, we see no ethical barriers to performing the RCT in our study population. Importantly, we will not include patients that have an eGFR of < 30 ml/min/1.73m2 even though in all probability even these patients will not be at greater risk without intravenous hydration, and we will include only those procedures involving non-ionic low osmolality monomer contrast material.

Patient risk: extra precautions taken
Despite the evidence, uncertainties and questions laid out above, we wish to take seriously the warning that the occurrence of CIN may imply for the potential occurrence of clinically relevant effects. Therefore, any patient diagnosed with CIN will be closely monitored.

If renal function has not normalised at 10-14 days after the contrast procedure, as would normally be expected, or if a patient*s eGFR drops below 30 ml/min/1.73m2 or if a patient*s eGFR decreases by *10ml/min/1.73m2, we shall inform the referring physician.

A data safety monitoring board (DSMB) will further ensure patient safety, and the trial will be monitored according to ICH-GCP guidelines by the Clinical Trial Centre Maastricht (CTCM).

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 *18 years of age, with moderate renal insufficiency (eGFR *30ml/min/1.73m2), referred for prophylactic intravenous hydration before and after an elective contrast procedure.

Exclusion criteria

emergency or intensive care patients, patients receiving or having received renal replacement therapy, patients with severe renal insufficiency (eGFR <30ml/min/1.73m2), patients <18 years of age, patients unable or unwilling to personally give informed consent

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-06-2014
Enrollment:	1370
Type:	Actual

Ethics review

Approved WMO Date:	14-05-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-06-2016
Application type:	Amendment
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
ClinicalTrials.gov	NCT02106234
CCMO	NL47173.068.14

Study results

Date completed:	18-08-2017
Results posted:	15-05-2017
Actual enrolment:	660

Summary results
Trial is onging in other countries

First publication
20-02-2017