Supplement 1 Trial Protocol

A randomized study on increased efficacy of prevention of contrast nephropathy

The Kompas study

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Synopsis

Introduction: Contrast nephropathy (CIN) may occur after administration of iodine containing contrast fluid for the purpose of making a CT scan. After the onset of CIN, kidney function is almost always restored within two months. The CBO guideline recommends that at risk patients (estimated renal function (eGFR) < 45 ml/min OF eGFR 45-60 ml/min in combination with co-morbidity) be treated with 1000 ml of 0.9% sodium chloride (NaCl) per drip 3-12 hours before and 3-12 hours after the study. The likelihood of contrast nephropathy and permanent renal injury is very low in the group of patients with mild renal insufficiency (estimated renal function 30-60 ml/min). However, due to the hydration, these patients are admitted for one to three days when they have undergone a CT scan. The implementation of the CBO guideline is therefore experienced in clinics as cumbersome and very expensive (in the Netherlands annual costs: 25.9-39.0 million Euros). Previously, a randomised study was carried out which showed that prehydration with sodium bicarbonate is non-inferior to pre- and posthydration with NaCl in patients with an indication for preventive hydration according to the CBO guideline.

Purpose: To evaluate whether the CBO indication for preventive hydration can safely be shifted from an eGFR < 45 ml/min or an eGFR 45-60 ml/min in combination with risk factors for CIN to an eGFR < 30 ml/min.

Study design: Multi-center randomized non-inferiority study.

Patients and method: Patients undergoing CT scan with intravenous administration of iodine contrast agents and an eGFR 30-45 ml/min or an eGFR 45-60 ml/min in combination with diabetes mellitus (DM) or at least two of the CBO risk factors for contrast nephropathy are asked to participate in this study. A total of 574 patients are needed. The patients are randomly divided between the following two study arms:

- Group 1: Prehydration with sodium bicarbonate 250 ml, 1.4%, 1 hour before CT.
- Group 2: No preventive hydration

Diagnostic tests: Kidney function and markers for kidney injury are measured prior, 2-4 days, 7-14 days and, on indication, 2 months after performing a CT scan.

Study endpoints:

Primary:

1. Average relative increase in serum creatinine 2-4 days after contrast administration.

Secondary:

1. CIN defined as an increase in serum creatinine > 25% or > 44 µmol/l after 2-4 days;
2. Average relative increase in serum creatinine 7-14 days after contrast administration;
3. Rehabilitation of renal function in CIN patients after two months;
4. Acute renal failure according to serum creatinine based RIfle criteria (see appendix)
5. Number of patients who develop an indication of dialysis;
6. Re-admission and duration of re-admission in the 2 months after randomisation;
7. Number of outpatient contacts in the 2 months after randomisation.

Endpoints of economic analysis:

- The additional costs of preventing one case of contrast nephropathy with prehydration compared to the absence of preventive hydration;
- Annual cost savings for preventive hydration in the Netherlands when the proposed new indication would be introduced.

Background

CT scan with iodine contrast agent is often used as a diagnostic tool in patients with a suspicion of malignancy, metastasis, inflammatory processes in the abdomen or thorax or in the diagnosis of peripheral vascular disease. In this study, patients are at risk of developing contrast nephropathy (CIN), an acute impairment of kidney function. CIN is defined as an increase in creatinine of at least 25% or at least 44 µmol/l occurring 2 to 4 days after the contrast administration.[1] Patients with pre-existing renal impairment have an increased risk of developing contrast nephropathy.[2]
According to the guideline of the CBO "Iodine Contraindicants Precautions" (2007) also implemented in the VMS programme "Renal insufficiency in intravascular use of Iodine Contraindicants", patients with an estimated glomerular filtration rate (eGFR) < 45 ml/min or an eGFR 45-60 ml/min in combination with diabetes mellitus or at least two of the risk factors listed in Table 1, should be given both pre-treatment and after-treatment with 0.9% sodium chloride 1 ml/hr/kg body weight each for 12 hours or 3-4 ml/hr/kg body weight each for 4 hours. In practice, this is standardized to 1000 ml before and after the CT scan.[1] Pre- and post-treatment with a sodium chloride infusion reduces the risk of contrast nephropathy.[3,4] The mechanism of this protection is probably based on direct volume expansion resulting in increased diuresis. In most cases, patients are admitted for two days for preventive hydration in the case of an intravenous contrast-loaded CT scan, as a faster running-in time could lead to acute heart failure due to the rapid volume expansion. To determine renal function and thus the indication of pre-treatment with hydration, the eGFR is calculated using the Modification of Diet in Renal Disease (MDRD) formula.[5]

Risk factors	**Definition**
Peripheral vascular disease	
Heart failure	
Old age	Age > 75 years old
Anemia	Men Ht < 0.39, Women Ht < 0.36
Symptomatic hypotension	
High contrast volumes	> 150 cc
Reduced effective circulating volume	
Use nephrotoxic medication	Diuretics, NSAIDs, cyclosporine, tacrolimus, aciclovir, ganciclovir, amphotericin-B, aminoglycosides, cisplatin, phosphcarnet, vancomycin

Table 1. Risk factors for contrast nephropathy.

Purpose of the investigation

An important fact is that more than 25% of healthy 65-year-old men and 50% of healthy 65-year-old women have an eGFR < 60 ml/min.[6] Mild renal insufficiency in older patients may therefore not always be of clinical importance.[7] This is usually not an expression of kidney disease but a physiological loss of kidney function associated with ageing. It does, however, ensure that the group of patients who currently have an indication of hydration according to the CBO guideline is very large. Approximately 750,000 CT scans are made each year in the Netherlands using contrast agents, with approximately 100,000 to 150,000 patients needing kidney protection. This number will increase further as a result of the ageing of the population. All this is at the expense of the feasibility of the directive. Preventive hydration with sodium chloride in CT scans is perceived by patients as stressful due to the long duration of admission and also costs a lot of money (in the Netherlands annually between 25.9 and 39 million euros). In addition, this treatment has the disadvantage that a fluid overload in the body can occur, whereby patients can become acutely oppressive.
In addition to pre- and posthydration with sodium chloride, another treatment is also possible, namely only prehydration with 250 ml of 1.4% sodium bicarbonate. This treatment has been shown to be non-inferior to pre- and posthydration with sodium chloride in a LUMC-initiated multicentre randomised study in patients with an indication for preventive hydration according to the CBO guideline. The results of this study, called the Saliña Study (NTR2149), have not yet been published but show that both the incidence of contrast nephropathy and the average increase in serum creatinine are similar in the study arms (pre- and posthydration with NaCl or only prehydration with sodium bicarbonate).[8] None of the patients developed an indication of dialysis and the degree of recovery of renal function after the onset of contrast nephropathy was the same in both groups. Sodium bicarbonate prehydration is therefore a safe and inexpensive alternative to sodium chloride prehydration and posthydration.
The risk of permanent kidney damage from the administration of iodine-containing contrast agents is very low in patients with mild renal insufficiency. In only 1.1% of patients, renal function is still impaired 2 months after the CT scan and 0.06% of patients receiving intravenous contrast are temporarily on dialysis.[9] In the population with mild renal impairment, (eGFR 30-60 ml/min), the probability of CIN is between 0 and 1% when pre- and posthydration is applied.[10,11] Patients with an eGFR 30-60 ml/min are the largest group of patients with an indication of preventive hydration while they have a very low risk of developing CIN and an even lower risk of developing complications of CIN such as dialysis or permanent loss of renal function. For some time now, Dutch Internist nephrologists have been discussing the identification of CIN for pre- and posthydration, as was also reported in the journal Medical Contact.[12,13] If the indication for preventive hydration could be reduced to an eGFR <30 ml/min, this could result in approximately 70% savings in healthcare costs for preventive hydration.

The primary question of the Compass Study is as follows:
Can the current limit for the indication for preventive hydration safely be shifted from eGFR < 45 or eGFR 45-60 ml/min in combination with the presence of diabetes mellitus or at least two risk factors to eGFR < 30 ml/min regardless of the presence of risk factors?

Purpose of the investigation

The aim of the study is to analyse whether the current limit value for the indication for preventive hydration can safely be shifted from eGFR < 45 or eGFR 45-60 ml/min for more risk factors to eGFR < 30 ml/min regardless of the presence of risk factors.

Question

Is the mean relative increase in serum creatinine in the non-hydrogenated patient group not more than 10% higher compared to the patient group treated with preventive hydration, in the case of CT-

scan with intravenous contrast administration? The latter group will be prehydred with 1.4% 250 ml of sodium bicarbonate administered in one hour prior to the CT scan.

Design of the study

The study was designed as a prospective, non-inferiority, multicenter randomized study.

Study endpoints:

Primary:
1. Average increase in serum creatinine 2-4 days after contrast administration.

Secondary:
1. CIN defined as an increase in serum creatinine > 25% or > 44 µmol/l after 2-4 days;
2. Restoration of renal function in CIN patients two months after CT scan;
3. Average increase in serum creatinine 7-14 days after contrast administration;
4. Acute renal failure according to serum creatinine based Rifle criteria (see appendix)[14,15]
5. Number of patients who develop an indication of dialysis;
6. Re-admission and duration of re-admission in the 2 months after randomisation;
7. Number of outpatient contacts in the 2 months after randomisation.

Patients selection criteria

Inclusion criteria:

- Patients with an eGFR 30-45 ml/min;
- Patients with eGRF 45-60 ml/min and diabetes mellitus (type I and II);
- Patients with an eGRF 45-60 ml/min and at least two of the following risk factors: peripheral vascular disease, heart failure, age > 75 years, anaemia, contrast volume > 150 ml, or use of nephrotoxic medication;
- Informed consent.

Exclusion criteria:

- Patients under the age of 18;
- Patients with reduced effective circulating volume (symptomatic orthostatic hypotension or systolic blood pressure < 100 mm Hg);
- Patients with an eGFR < 30 ml/min;
- Patients who underwent contrast-fluid imaging studies < 7 days ago (including MRI contrast) or patients with a planned contrast-fluid administration in the 5 days following CT scan;
- Pregnancy;
- Patients who have undergone kidney transplantation in the last three years;
- Previously participated in the Compass Study;
- Patients with proven unstable renal function in the four weeks prior to randomization (increase or decrease in serum creatinine > 20%);
- Known allergy or hypersensitivity to iodized contrast agents.

Method

Randomization

For all patients who undergo a CT scan, creatinine and therefore the eGFR are determined in advance at the outpatient clinic. This eGFR value is used to screen patients for suitability for inclusion. Patients are included after the study has been explained to the patient and the statement of consent has been signed by him or her. The included patients are divided between two study arms after computer-controlled randomisation:
- Group 1: Pre-hydration with 250 ml of 1.4% sodium bicarbonate 1 hour before CT scan;
- Group 2: No hydration to prevent contrast nephropathy.
In addition, in accordance with the CBO guideline, all patients are advised to drink enough on the day of the CT scan.

Registration of patient data

Registered the following patient data:

- Age;
- Gender;
- BMI;
- Blood pressure;
- Hypertension (systolic > 140 mmHg, diastolic > 90 mmHg, or use of anti-hypertensive agents after a previous episode of hypertension);
- Wrist;
- Reason for CT-scan application (malignancy, peripheral vascular disease, etc.);
- Type of CT scan (abdomen, thorax, angiography, thoracic abdomens, urography, etc.);
- Kidney diseases or urological diseases in the past;
- Specification renal diseases/urological history (renal cell carcinoma, bladder carcinoma, ATN, prostate carcinoma, benign prostate hypertrophy, hernia, otherwise);
- Solitary kidney;
- Kidney transplant in the past;
- Year of kidney transplant;
- Risk factors for contrast nephropathy as mentioned in Table 1;
- Smoking behaviour, in number of pack-years;
- Use of medication and dosage;
- Stop medication for CT scan;
- Volume and concentration of contrast agent;
- Use of oral contrast (type and volume in liters)
- Time between CT and creatinine measurement 2-4 days after CT;
- Time between CT and creatinine measurement 7-14 days after CT;
- Haemoglobin, creatinine, urea, uric acid, phosphate;
- eGFR for contrast fluid administration;
- Urine albumin/creatinine ratio;
- Additional iv volume expansion, other than to prevent CIN;
- Total volume additional iv volume expansion in the 12 hours before and after CT scan;

- Protocol violation by:
    - o CT cancelled;
    - o No contrast with CT;
    - o (Other) infusion given (none, sodium bicarbonate, sodium chloride);
    - o Volume infusion if protocol violation.

The data are registered on a paper case report form and later entered into the electronic database (Promise).

Urine and blood collection

- T0: Prior to the CT scan, blood and urine are collected to determine markers of kidney function and damage: haemoglobin, urea, creatinine, the eGFR by means of the MDRD, uric acid, phosphate, and the albumin/creatinine ratio in the urine. The values of the above mentioned substances will be determined at the end of the study. Until then, the material is stored in a freezer with temperatures of at least -80°C. In addition, the serum creatinine is determined immediately upon absorption. The determination of serum creatinine is part of standard care.
- T1: 2-4 days after the CT scan, all patients return to the hospital for blood sampling. If the patient is still admitted after 3 days, the blood collection is arranged in the ward. After inclusion, all patients receive a special lab form with which these determinations can be requested. Patients who do not come to the hospital are called. If necessary, blood will be taken at home. In the laboratory the following is determined immediately: serum creatinine and eGFR by means of the MDRD. In addition, samples are stored to further determine serum creatinine, urea, uric acid, phosphate and albumin/creatinine ratio in the urine.
- This process of 2-4 days after CT is repeated 7-14 (T2) days after CT scan.
- If CIN is detected after 2-4 days, renal function will be monitored after 2 months (T3) using the following methods: plasma creatinine, eGFR by means of the MDRD. Also urine and serum samples are stored to determine the serum creatinine, urea, uric acid, phosphate and albumin/creatinine ratio.

Storage of laboratory equipment

All serum and urine samples collected for the Compass Study will be stored in a freezer. The samples are anonymously encoded. Only the researcher and research nurse can trace these codes back to the corresponding patients. The storage of this material has two purposes: first, at the end of the study, all lab material is remeasured for the primary and secondary endpoint at the CKCL of the LUMC. Secondly, the lab samples will be used in the future for research into the pathophysiology of contrast nephropathy. The exact research questions for this have not yet been defined.

Duration and scope of the study

Based on the results of the earlier Saliña Study, it is expected that with the participation of seven hospitals, the study can be carried out in 2 years.

Group size and feasibility

The study was set up as a non-inferiority study. Based on data from Saliña Study, it was found that after intravenous contrast administration, serum creatinine increases by an average of -2.0% at a standard deviation of 13%. It is stated that omission of preventive hydration is non-inferior to prehydration with 250 ml 1.4% sodium bicarbonate in patients with an eGFR 30-60 ml/min, when the difference in average serum creatinine increase between the groups is less than 10%. To detect a difference in average serum creatinine increase of at least 10% at a standard deviation of 20%, approximately 250 patients per study arm are needed at a power of 80%. This is the power under the assumption of an actual difference in serum creatinine increase of 5%. Taking into account a lost to follow-up of 15%, a total of 287 patients per arm will be included. This leads to a total study population of 574 patients.

Statistical analysis

- Calculate the mean percentage increase in serum creatinine 2-4 days after contrast administration. The difference between the two arms is estimated, along with a 95% confidence interval for this difference;
- Calculate the mean percentage increase in serum creatinine 7-14 days after contrast administration. The difference between the two arms is estimated, together with a 95% confidence interval for this difference;
- Comparing the incidences of CIN in both groups by means of an Odds Ratio with corresponding p-value;
- Comparing the number of CIN patients in which the renal function recovers in both groups by means of an Odds Ratio with corresponding p-value;
- Comparing the number of CIN patients that develop an indication of dialysis in both groups by means of an Odds Ratio with corresponding p-value.

Statistical analysis subgroups

Subgroup analyses will be carried out to the primary endpoint and the secondary endpoint of CIN. The proposed subgroups are patients with:
- eGFR 30-45 ml/min and two risk factors for CIN (see Table 1)
- Diabetes mellitus in combination with an eGFR 30-45 ml/min
- Age > 75 years

Efficiency analysis

In order to assess whether lowering the renal function threshold for the indication of preventive hydration leads to an increase in the number of re-admissions, hospital days and outpatient contacts up to 2 months after randomisation as a result of a possible minimal increased risk of CIN, this information will be retrieved for all patients in the hospital system.
In the cost analysis, in addition to the primary treatment (hydration with associated hospitalisation time), other hospital costs during the initial 2 months after randomisation will also be included (internist and nephrologist consultations and hospitalisation time). In a cost effectiveness analysis, these costs will be related to the risk of CIN (costs per prevented CIN).

Ethical considerations

Informed consent

Informed consent is requested from each patient after the study has been explained in detail and any possible consequences compared to current diagnostic practice have been clarified. Each patient must record his consent in writing on the form attached (see appendix). Withdrawal of consent by the patient is possible at any time during the study, regardless of the reasons for this and without adverse consequences for the patient.

Administrative procedures

The researcher assures the patient that anonymity for third parties is guaranteed. This is done because each patient is mentioned on the study forms only with a study number and his initials.

Independent doctor

Independent doctor for this study is Dr. J Fogteloo, internist, available on telephone number: 071-5262085.

Insurance

An insurance policy has been taken out for the test subjects

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