Efficacy and safety of forced diuresis and guided fluid replacement therapy on contrast media induced nephropathy; a feasibility study

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2.1 Primary Objective: To evaluate the feasibility of RenalGuard for diuresis-guided fluid replacement therapy (ability to match in and output) (time to desired diuresis>200ml/hour) To evaluate the safety of forced diuresis and fluid replacement...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON34419

Source
ToetsingOnline

Brief title
Forced diuresis and guided fluid replacement in CIN Prevention

Condition

- Coronary artery disorders
- Nephropathies

Synonym
kidney damage because of contrast agents

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W,PLC Medical Systems Inc

Intervention

Keyword: Contrast nephropathy, Feasibility study, Forced diuresis, Prevention

Outcome measures

Primary outcome

Main study parameter/endpoints

1. The development of contrast induced nephropathy defined as a rise in serum

creatinine of > 25% 48 to 72 hours after administration.

2. Development of overhydration/pulmonary edema or other adverse events;

hypotension or clinically significant changes in electrolytes

Secondary outcome

Secondary study parameters/endpoints (if applicable)

Ability to match in and output, time to desired diuresis >200ml/hour

Incidence of hypokaliemia

Logistics of protocol

Study description

Background summary

Contrast media are frequently used in diagnostic and therapeutic procedures.
The total number of procedures with contrast media amounts approximately 1 million/year in the Netherlands and is expected to increase in the nearby future.
Although replacement of high osmolar iodinated contrast media by low osmolar non-ionic contrast media has reduced the number of adverse events,

acute renal failure is still a regular and severe complication seen after intravascular administration of iodinated contrast media.
This contrast-induced nephropathy (CIN), defined as a rise of serum creatinine > 25% within 48 to 72 hours after administration of contrast media, is associated with marked morbidity and mortality.
It is therefore important to recognize the patients at risk and to take appropriate preventive measures.

Patients with pre-existing chronic kidney disease who receive high volume of (intra-arterial) contrast media are at highest risk of this contrast-induced nephropathy (CIN).

Although the exact mechanisms remain unknown, intravenous hydration before the catheterization procedure is the only current treatment that has shown to reduce the incidence of CIN.
However in patients with baseline impairments in renal or cardiac function, hydration is not without risk and preformed at a slow rate due to fear of overhydration and pulmonary edema.
Previous studies have used diuretics to increase urine output en prevent overhydration.
In addition to the benefit of increased urine flow, loop diuretics, such as furosemide, should be expected to provide benefit against another potential mechanism of CIN, medullary ischemia, as they reduce sodium reabsorption and consequentially oxygen consumption of the kidney.

However a number of studies have shown that the use of furosemide is associated with an increased risk of CIN. This was most likely the consequence of insufficient fluid replacement. (Renal failure was also associated with weight loss in the furosemide-treated group.)

A prospective randomized trial of prevention measures in patients with a high risk for CIN (PRINCE Study) demonstrated that inducing diuresis with a single dose of diuretic, while attempting to prevent dehydration by balancing urine output with matched intravenous fluid replacement, provided an protective benefit against CIN. More importantly it showed that no patient with a mean urine flow rate above 150ml/hour developed CIN with the need for dialysis.
In this trail matching fluid replacement and urine output started after the procedure. Thus, it can be possible that some patients were intravascular dehydrated prior to the start of matched fluid replacement.

The real-time measurement and matched fluid replacement design of the RenalGuard system is intended to ensure that a high urine flow is maintained before, during and after these procedures and that the risk of over-or-under hydration is minimized while preventing CIN.

Previous animal and human studies were performed by using both the RenalGuard system and by manually replacing urine output with a matched amount of saline,

conform this concept. With promising results.

A recent animal study extended the PRINCE methodology of continuous matching of urine output and hydration to maintain intravascular volume starting pre-catheterization and maintained for up to 4 hours after the last dose of radio contrast material. In these animals with pacing-induced heart failure to put the kidneys at risk for CIN, the investigators found that maintenance of urine output greater than the equivalent of 150 ml/hour prior to and during the 4 hour period with maintenance of intravascular volume reduced the incidence of radio contrast injury to the kidney by 80% compared to the control group.

A human study was also performed, with manual fluid balancing, to test this concept. Ten patients with renal impairment and at risk for CIN, who were scheduled to undergo elective cardiac catheterization, were treated with the therapy. The inclusion and exclusion criteria were aimed at identifying patients who would be expected to have a 20-30% risk of developing CIN. Patients were given an initial 250cc IV bolus of normal saline and then an IV bolus of 1mg/kg of furosemide. After this, urine volumes were measured at 15 - 30 minute intervals and an infusion pump was adjusted to replace the measured urine output ml for ml (plus an additional 50ml/hr) of normal saline. Urine rates ranged from 631 - 2163 ml/hr (mean = 1139+440 ml/hr). Of the 10 patients treated, only one developed CIN (as defined as a 25% increase of serum creatinine over baseline) with a 28% increase of serum creatinine over baseline. There were no serious or unanticipated adverse events including any clinically significant changes in electrolytes. Any protocol or therapy related events were minor, and did not result in any significant clinical sequelae.

A pilot study was conducted under IDE G060190.13 The study was designed to preliminarily investigate the safety and performance of the RenalGuard* System in up to 40 subjects. The study was approved at 4 clinical sites and enrolled 23 subjects. The RenalGuard System was used on patients undergoing a previously scheduled cardiac or peripheral catheterization procedure. The protocol involved connecting the patient to the RenalGuard System using a Foley catheter and a standard peripheral i.v. catheter. The system was then set to deliver a 250 cc bolus of normal saline over 30 minutes. When the bolus was completed, the patients received 0.5 mg/kg of furosemide to induce high urine flow and the system continued to balance infusion input to urine output. Patients were kept on the system for approximately two hours prior to their catheterization procedure, throughout the procedure and for four hours after the procedure. Urine rates for these patients averaged approximately 550 ml/hr at the time of first contrast dose.
No patient experienced hypotension or significant impairment of vital organ function during the RenalGuard Therapy.
No subjects required renal replacement therapy or experienced symptomatic hypervolemia/pulmonary edema. One patient had clinically significant arrhythmias, which was determined to be due to the catheterization procedure.

One subject remained hospitalized overnight, at the decision of the investigator, to monitor the subject*s potassium levels due to the large volume of urine output achieved. The subject was discharged the following morning and experienced no clinical sequelae. There were no infections recorded during the study.
The system was shown to match effectively in- and output. Two of twenty-one evaluable subjects showed a creatinine increase of >25%. An additional secondary endpoint was the percent of patients that reached the target urine output of 300 ml/hr or greater over at least 2 hours of treatment. Only one patient did not meet this endpoint, and this was thought to be due to the subject*s chronic diuretic use.

After this pilot study FDA approval was obtained to begin the pivotal trial for renal guard therapy: The Mythos study
Preliminary results:
The trial has enrolled 105 chronic kidney disease (CKD) patients undergoing elective or urgent percutaneous coronary interventions (PCI). Approximately 14% of the patients in the control group were determined to have acquired contrast-induced nephropathy (CIN), whereas only 4% of those who were treated with RenalGuard acquired CIN. Dr. Marenzi also reported that the incidence of in-hospital complications in the control group was 18%, compared to only 6% in the RenalGuard group, a statistically significant difference (p=0.05)

The rationale of diuresis-guided fluid replacement therapy is evident and the first data look promising. Before embarking on controlled clinical trials, a feasibility study is needed to assess the safety of this treatment , its applicability, and its potential advantages. This is the primary object of this study.

A secondary objective of this study is to obtain blood and urine samples that will allow
identification and evaluation of biomarkers for the early detection of CIN.
The hypothesis is that different serum and urine markers can predict kidney injury better than
the conventional serum creatinine and proteinuria.
Cystatine C, NGAL, alfamicroglobuline and L-FABP are investigated in a number of small
studies.
We would like to store blood en urine samples to investigate these, or possible new
biomarkers (with proteomic techniques) in the future.

This study aims;
1.To evaluate the feasibility of RenalGuard for diuresis-guided fluid replacement therapy (in our hospital)
2.To evaluate the safety of forced diuresis and fluid replacement therapy

3.To evaluate the potential benefits of forced diuresis and fluid replacement therapy
4.To obtain blood and urine samples that will allow identification and evaluation of
biomarkers for the early detection of CIN in the future

Study objective

2.1 Primary Objective:
To evaluate the feasibility of RenalGuard for diuresis-guided fluid replacement therapy
(ability to match in and output) (time to desired diuresis>200ml/hour)
To evaluate the safety of forced diuresis and fluid replacement therapy
(adverse events)
To evaluate the potential benefits of forced diuresis and fluid replacement therapy
(incidence CIN)

2.2 Secondary Objective(s):
To obtain blood and urine samples that will allow identification and evaluation of
biomarkers for the early detection of CIN

Study design

Feasibility Study

Intervention

The treatment consists of induced diuresis with matched hydration therapy, using the RenalGuard System. The purpose of matched fluid replacement is to provide sterile replacement solution to a patient in an amount matched (millilitre for millilitre) to the volume of urine produced by the patient.

Approximately 90 minutes prior to the planned catheterization procedure, the RenalGuard system will be set up as instructed in the User*s manual.

A standard peripheral i.v. catheter (minimum of 20G; pink) will be inserted for hydration. The system requires the use of a standard Foley catheter, which will be inserted to allow the measurement of urine produced by the patient.
As the system requires the use of a Foley catheter, if it is unable to be placed the subject will be withdrawn from the study and the patient will undergo their cardiological procedure using standard (hydration) hospital protocols.

A blood sample is taken and serum potassium, sodium, ureum and creatinine, Hb, Ht, albumine are measured.
When the potassium level is
<3,0 : the subject will be withdrawn from the study
3,0-4,0: 20mmol/L Kaliumchloride in every litre of NaCl 0,9% will be substituted
>4,0 : 10 mmol/L Kaliumchloride in every litre of NaCl 0,9% will be substituted

Subjects may partake oral hydration up to the point of the procedure.
The RenalGuard system will be started in *Replacement Mode* and also will be set to deliver a pre-hydration bolus of 250ml of normal saline solution over a time period of 30 minutes.
The system continues to operate in *Replacement Mode* until 4 hours after the last dose of contrast.

Once the initial bolus hydration is complete, and prior to entering the catheterization lab, the patient will receive 0,5 mg/kg-1.0mg/kg of furosemide intravenously. (depending on GFR) (See Appendix 1)
When the urine flow rate is >150ml/hour,the patient may receive the first dose of contrast media.
Additional doses may be given if during catheterization and/or up to 4 hours post catheterization, if the calculated urine output falls below 200ml/hour.
The additional doses are 0,5-1.0 mg/kg furosemide intravenously (according to initial doses), but no more than every hour. The maximum total amount of furosemide that may be given is 3 mg/kg.

Data will be collected at frequent intervals (see Table 2) a nurse practitioner will be available throughout the treatment period to record the data and to monitor the patient for any adverse events, particularly signs and symptoms of fluid overload.
Patient vital signs (heart rate, blood pressure, pulse oximetry) will be recorded every 60 minutes until the discontinuation of therapy.
All intake (iv, oral) and output (urine, emesis, diarrhea) will be recorded every 30 minutes.
The time of the first contrast dose and last contrast dose as well as the total dose of contrast will be collected.
In all patients, we will take blood samples at baseline, after 2 hours, between four and six hours after administration of contrast, daily for the time they remain in the hospital, and one sample between 48 and 72 hours after contrast. These samples will be analysed and stored for future analysis of biomarkers.
In all patients we will collect urine samples, a baseline sample, one sample 0-2 hours after contrast, 2-4 hours after contrast, 4-6 hours after contrast. These samples will be analysed and stored for future analysis of biomarkers.

Physical examination will be preformed prior to the catheterization procedure

and again 3-6 hours post procedure.

All results will be recorded on the appropriate Case Report Form (s).

Study burden and risks

Patients may be exposed to the risk of adverse effects as a consequence of their participation in this study. Many of these risks are substantially minimized by increased subject monitoring before, during, and after treatment. An adverse effect is defined as any undesirable clinical event occurring in a patient after treatment in this study. This includes adverse effects that are related to the use of the System (device related adverse effect), the Therapy (therapy related adverse effect as over- or underhydration, elektrolytdisturbances), those which occur during the study but are related to the patient*s underlying disease (adverse effect due to pre-existing condition), and those which occur during the study but are related to the planned cardiovascular catheterization procedure (adverse effect related to cardiovascular cath procedure).
(see 8.2 Adverse and serious adverse events)

Potential Benefits
No benefits can be guaranteed to the study participant. However, there may be direct and indirect benefits to the patient for their participation in the study. The presence of radio contrast-induced renal impairment is associated with problems ranging from transient impairments in renal function to the occurrence of end-stage renal disease and the need for dialysis. The patient may benefit from a complete or partial prevention of impairment of renal function. In addition, there is the added benefit of close patient monitoring that may be more than the standard of care before, during and after the patient's cardiovascular catheterization procedure. Finally, the information learned from this study may help in the evaluation and further development of this therapy that may be helpful in treating patients in the future.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein Zuid 8
65oo HB Nijmegen
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein Zuid 8
65oo HB Nijmegen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

(see table 1)
1.Male or female>18 years
2.Scheduled to undergo a non-emergent catheterization procedure, with or without additional other procedures (e.g. left ventriculography, imaging of grafts, stenting etc.)
3.A Mehran risk score > 6 (score 6-10 CIN risk: 14%)
Mehran Risk score:
Congestive heart failure* 5 (excluded)
Hypotension** 5 (excluded)
Intra-aortic balloon pump use 5 (excluded)
Age >75 yrs 4
Anemia*** 3
Diabetes mellitus 3
Contrast volume 1 for each 100 ml
Estimated glomerular filtration rate
(ml/min 1.73 m2) MDRD 2 for 40 to 60,
4 for 20 to 40,
6 for <20(excluded);* NYHA III/IV or history of pulmonary edema
** systolic blood pressure <80mmHg for 1 hour requiring inotropic support or IABP within 24 h periprocedurally
*** baseline Ht<39% for men, <36% for women

Exclusion criteria

(see table1)
1.Severe heart failure :NYHA III/IV or history of pulmonary edema.
2. Has documented respiratory insufficiency, dyspnoea at rest, oxygen saturation <90% on room air assessed on day of procedure.
3.Hypotension systolic blood pressure <110mmHg.
4.Significant arrhythmias which compromise subject*s hemodynamic state.
5.Intra-aortic balloon pump use.
6.eGFR (MDRD) <20 ml/min 1.73 m2
7.Active urinary tract infection/or recurrent urinary tract infection.
8.Abnormal bladder function.
9.Known inability to place a Foley catheter.
10.Change in GFR >25% in the last month
11.M Kahler/ M Waldenström.
12.Use of NSAID's, other nefrotoxic drugs, or drugs that interfere with creatinine handling (e.g. aminoglycosiden, cisplatinum, mannitol, lithium, trimethoprim).
13.Catheterization procedure requiring a direct renal injection of contrast or an injection into the descending aorta proximal to the renal arteries.
14.Requiring emergent catheterization.
15.Serum potassium concentration <3,0 mmol/L..
16.Subject has known hypersensitivity of furosemide.
17.Participation in another study in the past 30 days
18.If female subject is pregnant or breastfeeding.
19.Subject is unable to provide written informed consent.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	07-02-2011
Enrollment:	50
Type:	Actual

Medical products/devices used

Generic name:	RenalGuard
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	11-01-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
CCMO	NL33395.091.10