A randomized trial of saline hydration to prevent contrast nephropathy in chronic renal failure patients

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Abstract

Background. Contrast nephropathy (CN) is a common cause of renal dysfunction that may be prevented by saline hydration and by drugs such as theophylline or furosemide. Whether oral saline hydration is as efficient as intravenous saline hydration is unknown. The preventive efficacy of theophylline and furosemide for CN remains controversial. The purpose of the current study was to evaluate the efficacy of oral saline hydration and of intravenous saline hydration plus theophylline or furosemide for the prevention of CN.

Methods. We prospectively studied 312 patients with chronic renal failure (serum creatinine 201 ± 81 μmol/l, Cockcroft clearance 37 ± 12 ml/min/1.73 m²), who were undergoing various radiological procedures with a non-ionic, low osmolality contrast agent. Patients were randomly assigned to four arms. In arm A, patients received 1 g/10 kg of body weight/day of sodium chloride per os for 2 days before the procedure. In arm B, patients received 0.9% saline intravenously at a rate of 15 ml/kg for 6 h before the procedure. In arm C, patients received the same saline hydration as in arm B plus 5 mg/kg theophylline per os in one dose 1 h before the procedure. In arm D, patients received the same saline hydration as in arm B plus 3 mg/kg of furosemide intravenously just after the procedure.

Results. Patients were well-matched with no significant differences at baseline in any measured parameters. Acute renal failure, defined as an increase in serum creatinine of 44 μmol/l (0.5 mg/dl), occurred in 27 out of 312 patients (8.7%). There was no significant difference between the rate of renal failure in the different arms of the study: five out of 76 (6.6%) in arm A, four out of 77 (5.2%) in arm B, six out of 80 (7.5%) in arm C and 12 out of 79 (15.2%) in arm D. No patient had fluid overload or a significant increase in blood pressure in the 2 days following the radiological procedure. The independent predictors of CN were diabetes mellitus, high baseline serum creatinine and high systolic blood pressure.

Conclusions. Oral saline hydration was as efficient as intravenous saline hydration for the prevention of CN in patients with stage 3 renal diseases. Furosemide and theophylline were not protective.

Keywords: contrast nephropathy; furosemide; randomized trial; renal failure; saline hydration; theophylline

Introduction

Contrast nephropathy (CN) is usually defined as acute renal failure occurring within 48 h of exposure to intravenous contrast media [1,2]. The frequency of CN depends on the definition of acute renal failure, the population studied, the type of radiological procedures, and the presence or not of risk factors [3]. CN is generally mild and reversible [4] but it can result in the need for dialysis treatment, extended hospital stays, and it contributes to morbidity and mortality, and to chronic end-stage renal failure [5].

Chronic renal failure, particularly in the case of diabetic nephropathy is the only independent risk factor in prospective studies [6,7]. Other factors characterized by reduced renal perfusion such as hypovolaemia or heart failure may also be involved [1,3].

Because radiological procedures involving contrast media are scheduled beforehand, the best treatment for CN is prevention [8]. Preventive measures include: avoidance of volume depletion, administration of anti-oxidant agents such as N-acetylcysteine [9,10],

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lower doses of contrast, avoidance of repetitive procedures and the use of low or iso-osmolar contrast media [11].

The optimal hydration, either the amount or the fluid to be used, isotonic saline or one-half normal saline [12] or sodium bicarbonate [13], has to be clarified. The best route to administer hydration, oral or intravenous, to prevent CN is not defined [14]. Drug interventions have also been tested in trials for prophylaxis against CN. Among these, are theophylline and furosemide. Theophylline, a non-specific adenosine receptor antagonist, was effective in animal studies to prevent the decline of the glomerular filtration rate after contrast injection [15,16]. However, clinical studies gave contradictory results [17,18] and recently a meta-analysis showed that the overall preventive effect of theophylline against CN was modest and probably clinically non-significant [19]. Furosemide has the potential to protect the kidneys in the face of renal insults but clinical studies in different models of acute renal failure including CN did not demonstrate a protective effect [20–23]. But the use of furosemide in the setting of CN prevention by volume expansion can reduce the risk of fluid overload.

We therefore performed a prospective, randomized trial to determine if oral saline hydration or intravenous saline hydration plus either theophylline or furosemide compared with intravenous saline hydration alone could decrease the incidence of CN in patients with chronic renal failure receiving contrast media during various radiological procedures.

Methods

Study population

Eligible patients were among those referred for any radiological procedures necessitating a contrast medium injection at Marseilles University Hospital, who had a baseline Cockcroft clearance between 15 and 60 ml/min (chronic kidney diseases stages 3 and 4). Patients were enrolled between May 2001 and October 2003. The patients included either had chronic renal failure on their own kidneys or on a kidney graft and whatever the aetiology of the chronic renal failure.

Exclusion criteria were patients <18-years-old, women of child-bearing potential not using a contraception, breast feeding women, patients with heart failure with ejection fraction <30%, uncontrolled arterial hypertension (blood pressure >180/110 mmHg), obvious extracellular overhydration, respiratory depression, known prior intolerance to theophylline or furosemide, and previous exposure to contrast media in the 14 days before randomization. For patients with a history of dyspnea and/or swelling, a pre-inclusion echocardiography was performed to assess left ventricular performance. Patients were also excluded if they were unwilling or unable to provide informed consent, adequate time prior to contrast media injection was not available to perform the study procedures, and if serum creatinine measurements varied by >10% in the previous weeks before referral.

The study protocol was approved by the local Ethics Committee: Comité Consultatif pour la Protection des Personnes relatif à la Recherche Biologique (CCPPRB). All patients gave written informed consent.

Study design

The study was an unblended, randomized controlled trial. Randomization was performed using a computer-generated randomization list known only to the research physician of the Centre d’Investigation Clinique (S.M.). Therefore, investigators were not aware of the next pending group assignment. Eligible patients were randomized in one of the four arms of the study 48 h before the radiological procedure (D–2). All the patients were asked to stop diuretics and non-steroidal anti-inflammatory drugs (NSAID) and to have a normal sodium chloride (around 6 g/day) and water intake during these 48 h. Other treatments, particularly renin-angiotensine blockers and calcium channel blockers were maintained. For patients with diabetes mellitus, biguanides were stopped and replaced by insulin.

In arm A, patients received 1 g/10 kg of body weight/day of NaCl per os for the 2 days before the procedure. NaCl was given to patients as 1 or 2 g capsules in two or three doses throughout the day. In arm B, patients received 0.9% saline intravenously at a rate of 15 ml/kg for the 6 h before the procedure. We considered arm B group as our control group. In arm C, patients received the same saline hydration as in arm B plus 5 mg/kg theophylline per os in one dose 1 h before the procedure. A short-acting theophylline was given since, according to the characteristics of the drug, the plasmatic peak is reached in about 30 min and the half-life is 5–6 h. In arm D, patients received the same saline hydration as in arm B plus 3 mg/kg of furosemide intravenously just after the procedure (Figure 1). Compliance to oral saline hydration in arm A was assessed by capsules count at D0.

Radiological procedures were at the discretion of the radiologist or the cardiologist who were permitted to use sufficient contrast media necessary to gain images. Only low osmolality non-ionic contrast media were used, mainly Hexabrix® (sodium and meglumine ioxaglate, Guerbet, Roissy, France), Xenetic® (iobitridol, Guerbet, Roissy, France), and Ultravist® (iopromide, Schering SA, Lys-lez-Lannoy, France).

Data collection

Demographic information was gathered at baseline, including age, gender, prior history of diabetes mellitus, hypertension, cardiovascular disease, heart failure and history of chronic renal failure. We also collected medications: anti-diabetics, immunosuppressants and anti-hypertensives. Other pertinent data were patient’s weight, BMI, blood pressure and evaluation of the extracellular volume. Blood pressure, evaluation of the extracellular volume, and adverse effects of the saline hydration and of medications were recorded 24 and 48 h after the procedure.

That very day and 24 h (D1) and 48 h (D2) following radiological procedures, serum creatinine and electrolytes were recorded. As we did not ask all the patients to collect urine 24 h after the procedure, information on urinary Na and volumes were available for only 120 patients.
Study endpoints

The primary endpoint was the number of CN in each arm. CN was defined as an increase in the baseline serum creatinine concentration of at least 44 \( \text{mol/l} \) (0.5 mg/dl) within 48 h after the injection of contrast media. We also evaluated the alteration of serum creatinine and the number of patients with fluid overload in each arm.

Statistical analysis

The SAS package was used for statistical analysis. Data were analysed by using the ANOVA procedure for continuous variables and Fisher’s exact test for categorical variables. The CN was compared between groups by using Chi 2-test. All tests were two-sided. A non-inferiority study was performed as a secondary analysis [24–26]. According to the trial of Solomon et al. [20], the absolute difference between saline hydration and saline hydration plus mannitol was 17% [95% confidence intervals (CI) 10.2–25.8%]. By comparison with saline hydration intravenously, we defined non-inferiority as a difference in CN <10%. Multivariate testing was conducted by logistic regression.

All results are presented as mean±SD. Differences were considered statistically significant at a \( P \) level of 0.05.

Results

A total of 315 subjects were enrolled, but one patient did not have contrast medium injection and two were lost for follow-up. Thus, 312 patients completed the study and were included in the final analysis. The mean age was 64 ± 14 years, 217 (70%) patients were men, 99 (32%) had diabetes mellitus, 252 (80%) had chronic renal failure on their own kidneys and 60 (20%) on a kidney transplant. Causes of chronic renal failure were chronic glomerulonephritis (\( n = 69, 22\% \)), interstitial nephritis (\( n = 24, 7.7\% \)), hypertension (\( n = 83, 27\% \)), others (\( n = 68, 22\% \)) and undetermined (\( n = 68, 22\% \)). Previous cardiovascular disease (stroke, myocardial infarction, aortic aneurysm and peripheral arteritis) was present in 142 patients (46%) and 55 (17.7%) had heart failure (ejection fraction \( \leq 40\% \)). The radiological procedures were coronaryography or angiography in 108 (35%) patients and tomodensitometry in 174 (56%) patients. Other radiological procedures were intravenous urography (\( n = 6 \)), phlebography (\( n = 6 \)), pulmonary angiography (\( n = 15 \)) and fistulography (\( n = 3 \)). Baseline serum creatinine was 201 ± 81 \( \text{mol/l} \), and Cockcroft clearance 37 ± 12 ml/min/1.73 m\(^2\).

Baseline characteristics for the patients in the four arms of the study are displayed in Table 1. Patients were well-matched with no significant differences at baseline in any measured parameters. The percentage of patients with diabetes mellitus or heart failure as well as baseline serum creatinine and Cockcroft clearance was similar in the study groups. The mean dose of contrast medium was not different in each arm.

Acute renal failure, defined as an increase in serum creatinine of 44 \( \text{mol/l} \) (0.5 mg/dl), occurred in 27 out of 312 patients (8.7%). There were no significant differences between the rate of CN in the different arms of the study: five out of 76 (6.6%, 95% CI 2.2–14.7) in arm A, four out of 77 (5.2%, 95% CI 1.4–12.8) in arm B, six out of 80 (7.5%, 95% CI 2.8–15.6) in arm C, and 12 out of 79 (15.2%, 95% CI 8.1–25.0) in arm D (Figure 2) (\( P > 0.05 \)). According to the non-inferiority test, the rate of CN was not inferior in arm B in comparison with those in arms A and C (\( P = \text{NS} \)), but it was inferior in comparison with arm D (\( P < 0.05 \)).
An increase in serum creatinine of 88 μmol/l (≥1 mg/dl) was found in only 11 out of 312 patients (3.5%): three in arm A, one in arm B, two in arm C and five in arm D. An increase in serum creatinine of 176 μmol/l (≥2 mg/dl) was observed in one patient. No patient required haemodialysis support. The mean change in serum creatinine concentrations, Cockcroft clearances and GFR estimate by MDRD formula at baseline (D0) and at 24 h (D1) and 48 h (D2) post-radiological procedure were non-significantly different in each arm (data not shown).

No patient had obvious fluid overload or a significant increase in blood pressure requiring antihypertensive treatments in the 2 days following the radiological procedure. Weight gains were +0.56 ± 0.52 kg between D-2 and D1 in arm A, +0.13 ± 0.12 kg between D0 and D1 in arm B, −1.14 ± 0.7 kg between D0 and D1 in arm C, and −0.46 ± 1.25 kg between D0 and D1 in arm D (P = NS for intra-group and inter-group comparisons). Alterations of 24 h urinary Na excretions, available for only 120 patients, are displayed in Table 2. Intra-group and inter-group 24 h urinary Na alterations were not statistically different except for group D between D0 and D1 (P < 0.05).

No adverse effects were reported by patients in the theophylline and furosemide arms. One patient had vomiting in arm A.

By univariate analysis, predictors of CN were an elevated baseline serum creatinine, the presence of diabetes mellitus, an older age and a high baseline blood pressure. Calcium antagonist treatment was protective. Importantly the volume of contrast medium, the type of radiological procedures and heart failure were not risk predictors. By multivariate analysis, diabetes mellitus, an elevated baseline serum creatinine, and an elevated baseline blood pressure remained independent predictors of CN (Table 3).

**Discussion**

The overall rate of CN was low (8.7%) in this study even though it was conducted in high-risk patients.

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**Table 1.** Demographic characteristics of the patients with chronic renal insufficiency in the four treatment groups

<table>
<thead>
<tr>
<th>Characteristic (mean ± SD)</th>
<th>Arm A (n = 76)</th>
<th>Arm B (n = 77)</th>
<th>Arm C (n = 80)</th>
<th>Arm D (n = 79)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 15</td>
<td>64 ± 11</td>
<td>65 ± 14</td>
<td>66 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>50/26</td>
<td>58/19</td>
<td>61/19</td>
<td>48/31</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 ± 15</td>
<td>72 ± 14</td>
<td>72 ± 16</td>
<td>71 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136 ± 20</td>
<td>138 ± 20</td>
<td>143 ± 26</td>
<td>147 ± 50</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76 ± 11</td>
<td>77 ± 12</td>
<td>77 ± 13</td>
<td>73 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic renal failure own kidneys/kidney graft</td>
<td>60/16</td>
<td>66/11</td>
<td>64/16</td>
<td>62/17</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>27 (35)</td>
<td>17 (22)</td>
<td>27 (33)</td>
<td>28 (35)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>18 (23)</td>
<td>11 (14)</td>
<td>12 (15)</td>
<td>14 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>63 (83)</td>
<td>64 (83)</td>
<td>72 (90)</td>
<td>64 (81)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>190 ± 65</td>
<td>208 ± 84</td>
<td>214 ± 113</td>
<td>201 ± 81</td>
<td>NS</td>
</tr>
<tr>
<td>Cockcroft clearance (ml/min/1.73 m²)</td>
<td>38 ± 15</td>
<td>33 ± 11</td>
<td>33 ± 14</td>
<td>34 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>GFR estimate by MDRD formula</td>
<td>34 ± 11</td>
<td>33 ± 10</td>
<td>35 ± 12</td>
<td>32 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Coronarography or angiography, n</td>
<td>29</td>
<td>22</td>
<td>29</td>
<td>28</td>
<td>NS</td>
</tr>
<tr>
<td>Tomodensitometry, n</td>
<td>40</td>
<td>46</td>
<td>46</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretic therapy n (%)</td>
<td>30 (39)</td>
<td>32 (42)</td>
<td>35 (43)</td>
<td>36 (45)</td>
<td>NS</td>
</tr>
<tr>
<td>ACEi or ARB, n (%)</td>
<td>22 (29)</td>
<td>27 (35)</td>
<td>24 (30)</td>
<td>19 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium channel antagonist, n (%)</td>
<td>25 (33)</td>
<td>20 (26)</td>
<td>29 (36)</td>
<td>27 (34)</td>
<td>NS</td>
</tr>
<tr>
<td>Volume of contrast medium (ml)</td>
<td>120 ± 40</td>
<td>115 ± 57</td>
<td>133 ± 70</td>
<td>119 ± 42</td>
<td>NS</td>
</tr>
</tbody>
</table>

GFR: glomerular filtration rate; MDRD: modification of diet in renal disease; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

**Table 2.** 24 h urinary Na excretions in the four treatment groups between baseline and D1

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Group</th>
<th>n</th>
<th>Group</th>
<th>n</th>
<th>Group</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29</td>
<td>B</td>
<td>30</td>
<td>C</td>
<td>32</td>
<td>D</td>
<td>29</td>
</tr>
<tr>
<td>24 h urinary Na baseline</td>
<td>73 ± 53</td>
<td>77 ± 55</td>
<td>73 ± 43</td>
<td>80 ± 55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h urinary Na D1</td>
<td>101 ± 73</td>
<td>122 ± 81</td>
<td>104 ± 85</td>
<td>238 ± 147</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ urinary Na (D1-baseline)</td>
<td>28 ± 65</td>
<td>45 ± 75</td>
<td>31 ± 55</td>
<td>158 ± 130</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are mmol/day. Baseline is D-2 for group A, and D0 for groups B, C and D. The intra-group and inter-group 24 h urinary Na alterations were not statistically different except for group D between D0 and D1 (P < 0.05).

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**Fig. 2.** Prevalence of CN in the four arms of the study.
This feature is slightly lower than the range observed in patients with a similar level of renal failure [11,20]. This can be explained by the meticulous preparation of the patients in the four arms of the study. In fact all the patients were asked to stop diuretics and NSAIDs, and all had a normal NaCl intake for the 2 days before the radiological procedure. These simple measures for preventing CN are too often neglected [27] and this neglect may lead to CN. Furthermore, they received high NaCl intakes either by an oral or intravenous route according to the protocol. The lower than anticipated CN rate could also be due to the high percent of patients having tomodensitometry, who in general have a lower CN rate than coronary or other arteriography patients [5]. Saline hydration was in all cases well tolerated without any significant episodes of fluid overloading. This result confirmed the efficacy and the safety of saline hydration in the prevention of CN [1,2,7,8,12,14,20].

The most important finding of this study was that oral saline hydration was not inferior as intravenous saline hydration. Only two controlled trials have challenged the efficacy of oral hydration for CN prevention [28,29], review in [30]. In one study, patients undergoing cardiac catheterization received either intravenous 0.45% saline solution at 75 ml/h for 12 h pre- and post-catheterization or oral hydration (1000 ml over 10 h) followed by 6 h of intravenous hydration with 0.45% saline at 300 ml/h beginning just before contrast exposure. There was no difference in the maximal change in serum creatinine between the two groups [28]. In another trial, CN was significantly more common in patients allowed to take unrestricted oral fluids in comparison with 24 h of intravenous normal saline at a rate of 1 ml/kg/h [29]. The lack of efficacy of water-based hydration in the latter study contrasts with the efficacy of NaCl-based hydration. This may be explained by a better compliance to NaCl. In fact, NaCl was easy to take and no adverse effects were observed. An alternative explanation is that patients had larger water intake due to the increase in serum osmolality following NaCl ingestion but we did not measure 24 h diuresis for all the patients.

This result was obtained in a large population of patients with renal failure including kidney transplant recipients. We only excluded patients with obvious overhydration, uncontrolled hypertension and severe heart failure (ejection fraction <30%), reinforcing the broad external validity of our results.

We did not have a hard parameter to verify the amount of hydration in the four arms because we did not ask all the patients to collect urine 24 h before and after the procedure. Looking at the patient's weight, no statistical difference was observed during the study between the different groups. Urinary Na excretions were also comparable between baseline and D1 in groups A, B and C. In group D, the significant increase in urinary Na was obviously due to furosemide. The similar weight and urinary Na alterations in the four treatment groups were arguments for a similar volume status whatever the saline hydration administered. In group A, non-compliance was unlikely since all the patients received strong information about the rationale of oral saline hydration. Furthermore capsule count at D0 did not reveal non-compliance.

The implication of the efficacy of oral saline hydration is that patients can be prepared for scheduled radiological procedures with contrast medium injection on the basis of outpatient conditions. This is particularly convenient for the patients, and a cost-saving procedure.

In the setting of toxic renal failure prevention, furosemide may protect the kidneys since it inhibits sodium tubular transport, reducing energy requirements of cells in the thick ascending limb of Henle [31]. It also reduces tubular–glomerular feedback thus preventing a decrease in the glomerular filtration rate [32]. Finally, it may flush out intratubular casts, reducing tubular obstruction [33]. But we confirmed that furosemide was not protective but detrimental for the prevention of CN. This study provides new evidence that furosemide is harmful to prevent toxic acute renal failure [20,23,34]. Furosemide could have been useful to avoid acute fluid overload. As we did not observe such fluid overload in the arms A, B and C, furosemide seems useless in this setting.

We did not observe an additive protective effect of theophylline to saline hydration. It is possible that the effect of theophylline was not apparent because of the major protective effect of saline hydration.

We showed that renal failure and diabetes mellitus were potential predictors of CN [35–37], but not the volume of contrast medium. Several studies have demonstrated a significant correlation between CN and contrast medium volume [5,37,38], although in other studies no such relationship was found [34–35,39]. The causes of this discrepancy are not obvious but may be related to study design and/or to the differences in patients and/or to the type of radiological procedure. As in one previous study, high blood pressure was an independent predictor of CN [35]. One possible explanation is that if high blood pressure reflects renal vascular disease, the renal vasoconstriction induced by contrast medium may be particularly deleterious and further compromise renal plasma flow and glomerular filtration rate.

### Table 3. Risk factors for CN by logistic regression

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2.4</td>
<td>0.05</td>
<td>1.001–5.6</td>
</tr>
<tr>
<td>Baseline serum creatinine</td>
<td>1.005</td>
<td>0.02</td>
<td>1.001–1.009</td>
</tr>
<tr>
<td>Baseline blood pressure</td>
<td>1.025</td>
<td>0.009</td>
<td>1.006–1.045</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>0.58</td>
<td>NS</td>
<td>0.23–1.42</td>
</tr>
<tr>
<td>Age</td>
<td>1.114</td>
<td>NS</td>
<td>0.79–1.57</td>
</tr>
</tbody>
</table>

All the variables that predict CN by univariate analysis were included in the multivariate analysis: baseline serum creatinine, age, diabetes mellitus, baseline blood pressure and calcium antagonist.
Study limitations

The study was initially powered to demonstrate the putative superiority of theophylline or furosemide over intravenous saline hydration. But as an interim analysis did not reveal such a superiority, we focused on the secondary endpoint of the non-inferiority of oral hydration over intravenous hydration. This non-inferiority was demonstrated but a correctly powered trial is necessary to confirm this result.

Conclusion

As oral saline hydration was as efficient as IV saline hydration, patients can be prepared for scheduled radiological procedures with contrast medium injection on the basis of outpatient conditions.

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