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INtravenous Contrast computed tomography versus native computed tomography in patients with acute Abdomen and impaired Renal functiOn (INCARO): a multicentre, open-label, randomised controlled trial - study protocol

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ABSTRACT

Introduction CT is the primary imaging option for acute abdominal pain in adults. Intravenous (IV) contrast media use improves CT quality but may cause post-contrast acute kidney injury (PC-AKI). Retrospective studies show no association between reduced baseline renal function and IV contrast CT, but, to our knowledge, no data from randomised controlled trials exist.

Methods and analysis The INCARO (INtravenous Contrast computed tomography versus native computed tomography in patients with acute Abdomen and impaired Renal functiOn) trial is a multicentre, open-label, parallel group, superiority, individually randomised controlled trial comparing IV contrast-enhanced CT to native CT in patients requiring emergency abdominal or body CT with impaired renal function defined as an estimated glomerular filtration rate (eGFR) of 15 to 45 mL/min/1.73 m^2. The primary outcome is a composite of all-cause mortality or renal replacement therapy (RRT) within 90 days from CT. Secondary outcomes are AKI measured by KDIGO (The Kidney Disease: Improving Global Outcomes) criteria within 72 hours from CT, organ dysfunction defined by mSOFA (modified Sequential Organ Failure Assessment) criteria after 48 hours from CT, alive and hospital-free days within 90 days after CT, and time from imaging to definitive treatment. All-cause mortality, need for RRT and renal transplant in long-term follow-up are also measured. The calculated sample size is 994 patients. Patient recruitment is estimated to take 3 years.

Ethics and dissemination The Ethics Committee of Helsinki University Hospital approved the study. The findings will be disseminated in peer-reviewed academic journals.

Trial registration number NCT04196244

Strengths and limitations of this study

- To our knowledge, the INCARO (INtravenous Contrast computed tomography versus native computed tomography in patients with acute Abdomen and impaired Renal functiOn) trial is the first randomised controlled trial examining the diagnostic strategy of acute abdomen using intravenous (IV) contrast CT versus native CT in a growing population of patients with impaired renal function.
- The prospective study setting and randomisation will minimise the selection bias associated with previous retrospective studies, and multicentre trial permits the formation of larger and more reliable patient cohort.
- Due to comprehensive registry data, it is possible to evaluate long-term effects of IV contrast exposure.
- As in the former studies, kidney injury evaluation is mainly based on estimated glomerular filtration rate values that are not optimised for acute kidney injury evaluation.

INTRODUCTION

The primary imaging option for the radiological diagnosis of acute abdominal pain in adults is CT. CT imaging commonly utilises iodinated intravenous contrast media that improve image quality. In most abdominal pathologies, intravenous contrast media enable more accurate imaging and increase the sensitivity and specificity of radiological diagnosis. Contrast media enhance the visualisation of various tissues. Contrast administration enables the detection of lesions from normal surrounding structures and the diagnosis of parenchymal and vascular pathologies. When diagnosing acute abdomen, contrast-enhanced CT is the gold standard

and, in most conditions, even mandatory for correct diagnosis. However, post-contrast acute kidney injury (PC-AKI), especially in patients with pre-existing renal insufficiency, has remained a significant concern among physicians for more than 60 years.[1 2] Earlier, the most common definition of PC-AKI was the increase of serum creatinine level to more than 44 umol/L or by 25% in 48 to 72 hours after contrast medium administration. Today, literature recommends KDIGO (The Kidney Disease: Improving Global Outcomes) criteria.[3] The pathophysiology of PC-AKI is complex and still poorly understood. According to present hypothesis, it is mediated by renal medullary hypoxia and direct cellular damage. Presence of endothelial dysfunction, for example, in diabetes mellitus, can further worsen these effects.[4]

A vast amount of early literature supports the existence of PC-AKI as a true clinical phenomenon. However, these studies are mostly retrospective, lack control groups and study intra-arterial instead of IV contrast administration.[5] In addition, modern iso-osmolality and low-osmolality contrast media are associated with lower risk of kidney injury than older high-osmolality contrast media.[6] Furthermore, the diagnosis of PC-AKI was typically based on the increase of serum creatinine level, although this increase seems equally common in patients not receiving intravenous contrast medium.[7]

More recent studies compare the incidence of PC-AKI in non-randomised designs between cohorts receiving contrast CT and native CT. In a recent meta-analysis, including 28 original articles and 107 335 patients, the incidence of PC-AKI varied between 2.1% and 26.4%. The meta-analysis did not show any differences between contrast-enhanced CT and native CT in AKI, mortality or dialysis rates.[8] Another recent meta-analysis studied 13 non-randomised studies with control groups representing 25 950 patients. Again, no differences between the contrast and non-contrast groups were detectable in AKI, mortality or dialysis rates. The result was similar even in patients with diabetes or chronic renal insufficiency.[5] Limitations of the findings include the retrospective and non-randomised nature of the studies leading to a risk of selection bias, non-standardised definitions of PC-AKI across the studies and lack of documentation of preventive actions such as pre-imaging and post-imaging hydration.

To decrease the selection bias, the newer studies use propensity score matching. A study with 12 508 propensity score-matched patients showed an association between diminished baseline estimated glomerular filtration rate (eGFR) and elevated post-imaging creatinine level diagnosed as AKI. However, the risk of AKI was independent of contrast administration, even in patients with eGFR below 30 mL/min/1.73 m^2.[9] Another propensity score-matched study with 20 242 patients showed an association of low-osmolality iodinated intravenous contrast and AKI in patients with eGFR below 30 mL/min/1.73 m^2. Patients with eGFR between 30 and 44 mL/min/1.73 m^2 showed a similar but not statistically significant trend. In patients with eGFR of over 45 mL/min/1.73 m^2, the contrast media appeared not to be nephrotoxic.[10] A recent propensity score-matched study from an emergency department with 17 934 patients showed no association between contrast media administration and AKI, not even with the lowest eGFR levels below 30 mL/min/1.73 m^2. In addition, the study did not show any association between contrast media administration and the incidence of chronic kidney disease, dialysis or renal transplantation at 6 months.[11]

Studies on PC-AKI in various patient populations exist: a recent study on the incidence of PC-AKI in patients with nephrotic syndrome found no association between contrast administration and AKI in any eGFR subgroup.[12] A retrospective study on trauma patients over 55 years of age found no difference between intravenous contrast and native CT in terms of PC-AKI.[13] A recent propensity score-matched study examined an intensive care unit (ICU) population of 6877 patients undergoing abdominal, pelvic or chest CT examination. Patients with pre-CT eGFR above 45 mL/min/1.73 m^2 showed no increase in PC-AKI, emergency dialysis or short-term mortality rates. However, patients with eGFR equal or below 45 mL/min/1.73 m^2 needed dialysis more often but no differences in post-CT AKI or 30-day mortality rates were seen.[14]

To summarise, a large amount of literature on PC-AKI exists, most of it retrospective and observational. The studies vary in definition of AKI and selection bias, which is a significant concern. In addition, retrospective study designs do not allow controlling for pre-scan and post-scan preventive actions, such as oral or IV hydration. Most studies show no association between intravenous contrast administration during CT examination and AKI, dialysis or mortality in any eGFR subgroups. However, the results vary in patients with eGFR below 45 mL/min/1.73 m^2. Earlier studies are summarised in online supplemental file.

The extensive use of CT imaging, the superiority of contrast-enhanced CT over native CT and the growing population of patients with compromised renal function set a tremendous need for a randomised controlled trial studying the safety of intravenous contrast administration during CT imaging in patients with impaired renal function. To the best of our knowledge, this would be the first randomised controlled trial on this subject.

Our research hypothesis is that IV contrast administration does not cause increased mortality or any organ failure in patients with compromised renal function (eGFR 15 to 45 mL/min/1.73 m^2) undergoing CT imaging for acute abdomen. By enhancing the diagnostic value of CT imaging, intravenous contrast administration could shorten the time to diagnosis and definitive treatment and, thus, improve patients' prognosis.

METHODS AND ANALYSIS

Study design

The INCARO (INtravenous Contrast computed tomography versus native computed tomography in patients

with acute Abdomen and impaired Renal functiOn) trial is a randomised prospective multicentre, open-label study recruiting in university and central hospitals in Finland. Participating hospitals are Helsinki University Hospitals Meilahti and Jorvi, and Hyvinkää Hospital. More hospitals may be added after the commencement of the trial. The trial is registered at ClinicalTrials.gov (NCT04196244). All participants will give written informed consent. Patient enrolment will be performed by all treating physicians. Most patients will be enrolled from hospitals' emergency departments, surgical wards and ICUs.

Inclusion criteria

Patients requiring emergency abdominal or body CT with eGFR 15 to 45 mL/min/1.73 m^2 will be screened for eligibility for this study. The eGFR is calculated from the last available plasma creatinine value taken a maximum 24 hours before randomisation.

Exclusion criteria

The exclusion criteria are: (1) age less than 18 years, (2) eGFR less than 15 or more than 45 mL/min/1.73 m^2, (3) renal replacement therapy (RRT) within 30 days prior enrolment, (4) CT with intravenous contrast less than 72 hours prior enrolment, (5) suspicion of vascular occlusion, dissection or bleeding (ie, need for IV contrast), (6) CT needed without IV contrast to detect or rule out ureteral stone, (7) intravenous contrast allergy, (8) pregnancy, and (9) no signed written informed consent.

Trial interventions

Intervention groups are:

1. abdominal or body CT with IV contrast, and
2. abdominal or body CT without intravenous contrast (native CT).

Both groups receive intravenous hydration with at least 3 mL/kg (equals 240 mL in 80 kg patient) of Ringer's lactate or 0.9% NaCl before and after contrast medium exposure. The pre-CT intravenous hydration is recommended to be infused over 3 hours and post-CT intravenous hydration over 4 to 6 hours. However, intravenous hydration may not postpone the CT scan if the treating physician deems CT necessary sooner. Laboratory tests are obtained before intervention and on post CT days 1, 2 and 3. If patients are discharged before 72 hours from the CT scan, they will be scheduled for a laboratory creatinine control on the third day after the CT scan. Figure 1 summarises the study flow.

Otherwise, the treatment of the patients is according to normal standard care in both groups. For example, the decision to admit patient to ICU or commence RRT are made according to each participating hospital's standard operating protocol. Repeat CT scans are allowed if deemed necessary by treating physician or surgeon,

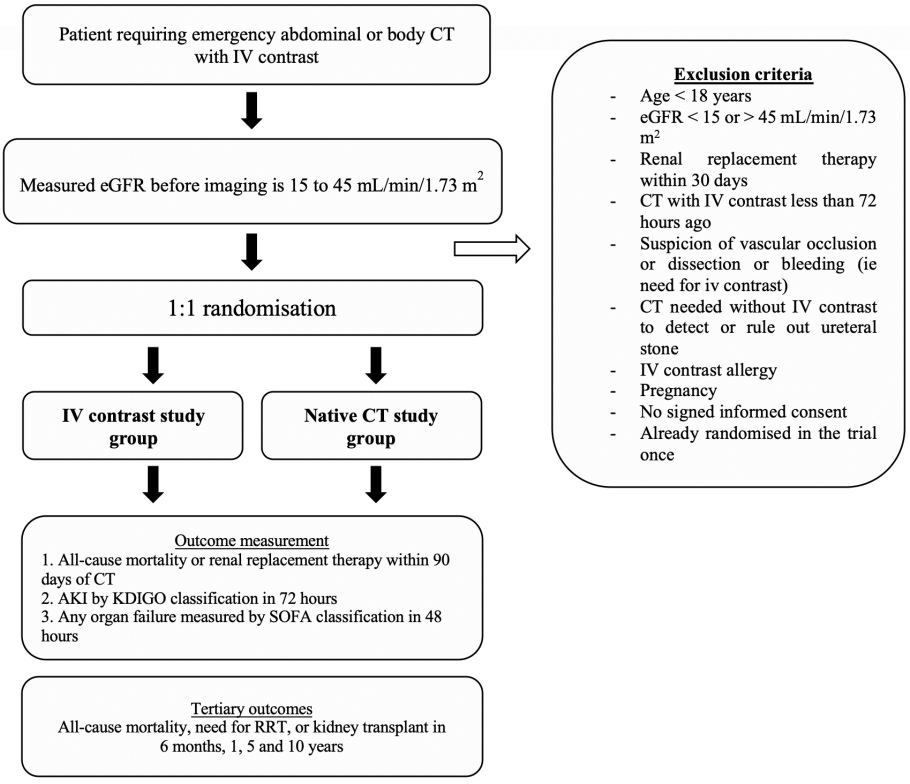

Figure 1 Flowchart of the INCARO trial. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; INCARO, INtravenous Contrast computed tomography versus native computed tomography in patients with acute Abdomen and impaired Renal functiOn; IV, intravenous; KDIGO, The Kidney Disease: Improving Global Outcomes; mSOFA; modified sequential organ failure assessment; RRT, renal replacement therapy.

Table 1 KDIGO classification stages for AKI based on creatinine level

Stage	Creatinine
1	1.5 to 1.9 times baseline or ≥26.5 µmol/L (≥0.3 mg/dL) increase
2	2.0 to 2.9 times baseline
3	3.0 times baseline or increase in serum creatinine to ≥353.6 µmol/L (≥4.0 mg/dL) or initiation of renal replacement therapy

AKI, acute kidney injury; KDIGO, The Kidney Disease: Improving Global Outcomes.

and these will be taken in account while analysing the outcomes.

Iodinated contrast media are administered according to hospital guidelines. The type and amount of contrast medium is recorded. Study hospitals normally use low-osmolality iodinated intravenous contrast medium (concentration 350 mgI/mL) for urgent and non-urgent abdominal and body CT. The amount of contrast medium is 1.5 mL/kg.

Randomisation

Patients will be randomised 1:1 to undergo either intravenous contrast CT or native CT. Randomisation sequence will be generated using a computer software with variable block size (4, 6 and 8) and will be concealed from recruiters, attending physicians, patients, data collectors and data analysts. Randomisation will be done using web-based computer system. Randomisation sequence will be stratified for:

- eGFR 15 to <30 vs 30 to 45 mL/min/1.73 m^2
- Patient age <65 vs 65 years or over
- Centre

As the attending physicians need to be able to analyse the CT images, the study is open-label. After a patient gives written informed consent, the attending physician performs randomisation and orders a CT scan.

Outcomes

The primary outcome is a composite that combines all-cause mortality and RRT within 90 days of CT. The secondary outcomes are: (1) the most severe AKI stage defined by the KDIGO plasma creatinine criteria (table 1)[15] within 72 hours after CT, (2) any organ dysfunction defined by at least two organ-specific mSOFA (modified SOFA) points (table 2) excluding central nervous system 48 hours after CT, (3) alive and hospital-free days within 90 days after CT and (4) time from CT to definitive treatment (ie, surgery, radiological intervention, endoscopy or medication) during hospital stay. Tertiary outcomes are all-cause mortality, RRT and renal transplant at 6 months, 1, 5 and 10 years after CT.

Sample size calculation

A previous study conducted at the Helsinki University Hospital on patients with diffuse peritonitis showed a 90-day overall mortality of 22%. In patients with eGFR less than 45 mL/min/1.73 m^2, the mortality was 39%. Patients with any perforation of the gastrointestinal (GI) tract had an overall mortality of 13%, whereas patients with eGFR less than 45 mL/min/1.73 m^2 had a mortality of 25%.[16] The documented incidence of AKI in hospitalised patients is 1.9%, and in ICU patients, the incidence exceeds 40%.[17] A recent meta-analysis of post-CT AKI showed an incidence of AKI of 7.17% in contrast CT group and 7.42% in native CT group. In contrast and non-contrast groups, RRT was necessary in 0.56% and 0.68% of patients, respectively.[8] The incidence of AKI after major abdominal surgery is 13.4% and rates of postoperative RRT vary from 0% to 3% between studies.[18] After general surgery procedure, the incidence of AKI is 1%, and the post-surgery RRT rate is 0.68%.[19] Risk factors for postoperative AKI include emergency surgery, intraperitoneal surgery, and mild or moderate renal insufficiency,[19] all leading to a higher than 1% rate of AKI and RRT.

All patients included in this trial will not have a GI tract perforation. Some patients might not have abdominal pathology, although it was suspected when ordering the CT scan. Thus, the mortality rate in the trial cohort will likely be lower than 25%. On the other hand, a composite outcome comprising all-cause mortality, RRT and renal transplantation will likely increase the rate of the primary outcome. We estimate that the primary outcome rate is 27% in the native CT group and 9 percentage points less (ie, 18%) in the intravenous contrast CT group. With

Table 2 Modified SOFA score

	0	1	2	3	4
Respiration	No support	Supplemental oxygen	NIV		Invasive ventilation
Coagulation (platelets; ×10^3/mm^3)	≥150	<150	<100	<50	<20
Liver (bilirubin; µmol/L)	<20	20 to 32	33 to 101	102 to 204	>204
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg			Vasoactive drugs used
Renal function (creatinine µmol/L)	<110	110 to 170	171 to 299	300 to 440	>440 or RRT

GCS (Glasgow coma scale) measurement is not included to this study.
MAP, mean arterial pressure; NIV, non-invasive ventilation; RRT, renal replacement therapy; SOFA, sequential organ failure assessment.

90% power and 5% alpha, the study requires 896 patients to show the difference. We estimate that 5% of patients randomised to native CT group will undergo intravenous contrast CT (cross-over from native CT to intravenous contrast CT group). Taking this into account, the final adjusted sample size will be 994.

Follow-up and data collection

The data and outcomes are recorded prospectively during the hospital stay using case report forms and electronic patient records. If patients are discharged before 72 hours from the CT scan, they will be scheduled for a laboratory creatinine control on the third day after the CT scan. Patients will be contacted on day 90, either at an outpatient visit or by telephone or mail. If a patient is transferred to another hospital during the 90-day period, electronic patient records are requested from that hospital, and outcomes are assessed using these records. In case no contact can be made or patient records are unavailable, the primary outcome can further be assessed using (1) Statistics Finland death registry (up to date registry for mortality), and (2) Finnish Registry for Kidney Diseases (up to date registry for permanent RRT). Follow-up data on tertiary outcomes at 6 months and 1, 5 and 10 years will be similarly assessed using these registries, and also from Transplantation Registry for renal transplantation.

Statistical analysis plan

This is a superiority trial. The analyses will be done in the intention-to-treat population. The null hypothesis for the primary and secondary outcomes is that there is no difference between the treatment arms. P value of less than 0.05 will be considered statistically significant and all analyses will be done two-tailed. The primary analyses will be performed using stratification variables (age <65 or ≥65 years, eGFR of 15 to <30 or 30 to ≤45 mL/min/1.73 m^2, and centre). Additionally, the crude outcomes will be reported.

The primary outcome will be analysed using logistic regression adjusted for the stratification variables. The effect size will be reported using risk ratio corrected from OR[20] with 95% CI.

The first and second secondary outcomes (AKI, any organ failure with mSOFA 2 or more) will be analysed using logistic regression adjusted for the stratification variables.

The third and fourth secondary outcomes (hospital free days, time to definitive treatment) will be analysed by using adjusted regression analysis where stratification variables are used as covariates.

Tertiary outcomes will be analysed when follow-up data for 6 months, 1, 5, and 10 years after CT are available, and will be reported using Kaplan-Meier curves with log-rank tests.

Prespecified subgroup analyses are defined by: (1) age (<65 or ≥65 years), (2) eGFR values (15 to <30 or 30 to 45 mL/min/1.73 m^2), (3) diabetes and (4) ongoing regular use of nephrotoxic medications preadmission (ACE (angiotensin-converting enzyme) inhibitors, AR (angiotensin II receptor) blockers, antimicrobial medications (aminoglycosides, cephalosporins, colistin, quinolones, rifampicin, sulfamethoxalone/trimethoprim and vancomycin) loop and thiazide diuretics, NSAIDs (non-steroidal anti-inflammatory drugs), COX-2 (cyclo-oxygenase-2) inhibitors, immunosuppressants and chemotherapy).

Schedule

Approximately 1100 (abdominal or whole body) emergent CT examinations without IV contrast media are performed in Helsinki University Hospital's Meilahti Hospital annually. We estimate that one-third could be recruited, meaning that approximately 300 patients could be recruited annually in Meilahti Hospital alone. Depending on the number of hospitals participating in the trial, we estimate the patient recruitment to take a maximum of 3 years. The estimated start of recruitment is autumn 2020.

Patient and public involvement

Patients were not involved in the design of the study or assessment of the burden of the interventions. On recruitment, patients are informed of the current knowledge on intravenous contrast administration during CT. The risks and benefits of the trial intervention are explained to the patients.

ETHICS AND DISSEMINATION

This study is approved by The Ethics Committee of Helsinki University Hospital. The study data validity and quality will be analysed by study monitoring personnel of Clinical Research Institute of Helsinki University Central Hospital.

All patients will sign a written informed consent after receiving oral and written information on the study. Study patients do not gain any financial benefit from participating in the study. They can cancel their participation at any time. In these cases, the information gathered before the cancellation will be used in the study.

PC-AKI has been a significant concern in patients with compromised renal function undergoing contrast enhanced CT imaging. Intravenous contrast improves image quality. Avoiding contrast administration may negatively impact patients' prognoses by leading to repetitive imaging that increases patients' total radiation load and delays diagnosis and treatment. Currently, the limit for more liberal intravenous contrast medium use is an eGFR level of 45 mL/min/1.73 m^2. However, growing amount of retrospective data suggests that the intravenous contrast administration is equally safe with lower eGFR levels. Randomised trials are necessary to confirm these findings.

Outside the study protocol, in participating centres, the standard imaging usually includes native CT for patients with GFR below 30 mL/min/1.73 m^2 and contrast-enhanced CT for patients with GFR between 30 to 45 mL/

min/1.73 m^2. Despite this, wide physician-specific variation in the decision between native or contrast-enhanced CT exists, and outside trials, this decision is up to the attending physician to make. A study patient randomised to the intravenous contrast group may have a slightly elevated risk of acute renal injury, but may gain more accurate imaging and prompt diagnostics, and possibly avoid repeated CT scans with extra radiation. On the contrary, a patient randomised to the native CT group could have a reduced risk of adverse renal events.

There are possible limitations regarding this study. First, the eGFR value is designed to measure kidney function in steady state which can be altered dramatically during the illness. To take this into account, the baseline creatinine value (the last creatinine value before the disease onset) will be recorded if available. Second, although this is a randomised trial, there are multiple confounders that cannot be standardised between the treatment groups. These include the post-CT hydration during the first 3 days after the randomisation as this is tailored based on the condition and diagnosis of the patient. Third, while the patient recruiting process is made as clear as possible, there is a risk for drop-out of patients. Especially patients who cannot sign the written consent or whose disease process mandates immediate CT imaging may not be recruited in the study.

To our knowledge, this is the first randomised controlled trial examining the association between intravenous contrast administration and patient outcomes. Safety interim analyses will be performed after the recruitment of 100 patients and at the halfway of recruitment. Interim analyses will consist of primary outcome, and secondary outcomes 1 to 3. The study can be prematurely stopped also for slow recruitment at researchers' discretion.

The study results will be published in peer-reviewed academic journals. The study protocol and results may be further disseminated via scientific conferences and social media platforms.

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