UNIVERSITAT DE BARCELONA

Eficàcia de la hidratació oral com a mesura preventiva de la lesió renal aguda postcontrast iodat

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UNIVERSITAT DE BARCELONA

TESI DOCTORAL

Eficàcia de la hidratació oral com a mesura preventiva de la lesió renal aguda postcontrast iodat

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Línia de recerca:
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Eficàcia de la hidratació oral com a mesura preventiva de la lesió renal aguda postcontrast iodat

Tesi doctoral presentada per **Carmen Sebastià Cerqueda**
per optar al grau de doctora per la Universitat de Barcelona

Dirigida per:

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Aquesta tesi s'ha realitzat a l'Hospital Clínic de Barcelona.
Servei de Radiodiagnòstic (CDI).

Programa de Doctorat: "Medicina i Recerca Translacional"

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Facultat de Medicina i Ciències de la Salut. Universitat de Barcelona.

Octubre 2021

Els directors de la tesi doctoral de la Dra. Maria Carmen Sebastià Cerqueda, titulada "Eficacia de la Hidratació oral com a mesura preventiva de la lesió renal aguda postcontrast iodat",

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Declarem:

que la tesi presentada per la doctoranda **Carmen Sebastià Cerqueda** per optar al grau de Doctora en Medicina ha estat realitzada sota la nostra direcció. Que en aquesta tesi doctoral s'han complert els codis ètics i de bones pràctiques i de que no tenim coneixement de que s'hagi produït cap plagi. Un cop finalitzada, els directors autoritzem aquesta tesi per a ser jutjada pel tribunal que correspongui.

I perquè en quedi constància als efectes oportuns, firmem la present a Barcelona, octubre del 2021.

Carlos Nicolau
Director

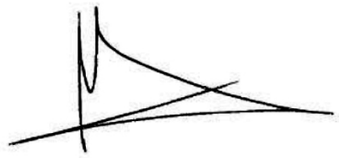
Laura Oleaga
Directora

DECLARACIÓ DE BONES PRÀCTIQUES DEL DOCTORANT

Jo, Maria Carmen Sebastià Cerqueda, amb DNI 41080033D, doctoranda, declaro que la tesi que diposito titulada "Eficàcia de la hidratació oral com a mesura preventiva de la lesió renal aguda postcontrast iodat":

- És una tesi original.
- S'han complert els codis ètics i de bones pràctiques.
- La tesi no conté plagi.
- Manifesto que coneixo i consento que la meva tesi sigui sotmesa a procediment per comprovar la seva originalitat.

Barcelona, 3 d'octubre del 2021



Maria Carmen Sebastià Cerqueda

Als meus pares, que amb el
seu esforç i recolzament
incondicional han aconseguit que
arribés fins aquí

Al Xesco, el Quim i el Lluc
per la paciència i l'amor

A tot el servei de
Radiodiagnòstic que d'una manera
o una altra ha estat implicat en
aquesta tesi, especialment a la
Sílvia i la Raquel

A tots aquells que amb el
seu exemple, ajuda i amistat m'han fet
millor professional
i millor persona

FINANCIACIÓ

Els estudis efectuats i publicats que són el fonament d'aquesta Tesi Doctoral han rebut una beca de la Societat Española de Radiologia Abdominal (SEDIA) com ajuda per sufragar les despeses del disseny de l'estudi prospectiu.

SEDIA 2021: 2000 euros

CONFLICTE D'INTERESSOS

Res a declarar

INDEX

GLOSSARI D'ABREVIATURES

ACR: American College of Radiology
AKI: acute kidney insuficiency
CA-AKI: Contrast-Associated Acute Kidney Insuficiency
CMSC: Contrast Media Safety Committee
CKD: chronic kidney disease
Cr: creatinina sèrica
ESMO: European Society of Medical Oncology
ESUR: European Society of Urogenital Radiology
FG: filtrat glomerular
i.v.: intravenós
IRC: insuficiència renal crònica
IRA: insuficiència renal aguda
LRA-PC: lesió renal aguda postcontrast
ml: mil·lilitre
MM: mieloma múltiple
µmol/l: micromol per litre
mg/dl: mil·ligrams per decilitre
NIC: nefropatia induïda per contrast
PC-AKI: Post-Contrast Acute Kidney Insuficiency
KDIGO: Kidney Disease Improving Global Outcomes
SERAM: Sociedad Española de Radiología
TC: tomografia computaritzada

GLOSSARI DE DEFINICIONS I CONCEPTES

Nefropatia induïda per contrast (NIC)

La nefropatia induïda per contrast (NIC) es defineix com l'empitjorament de la funció renal que apareix durant els tres dies posteriors a l'administració intravascular d'un mitjà de contrast iodat, en absència d'una etiologia alternativa, amb un increment del valor de la creatinina (Cr) major del 25% o 44,5µmol/l (0,5 mg/dl) (1).

Lesió renal aguda post contrast (LRA-PC)

La lesió renal aguda postcontrast (LRA-PC) es defineix com un increment de la creatinina (Cr) ≥ 0,3mg/dl (26,5µmol/l) o ≥ 1.5 vegades comparada amb el valor basal de la Cr que apareix entre les 48-72 hores després de l'administració intravascular del contrast iodat, en absència d'una etiologia alternativa. En anglès es coneix com a *post-contrast acute kidney insuficiency* (PC-AKI) o *contrast-associated acute kidney insuficiency* (CA-AKI) (2).

Estadis de la insuficiència renal crònica (IRC) segons la classificació de la Kidney Disease Improving Global Outcomes (KDIGO):

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Font de la imatge (3). En el nostre estudi valorem els pacients amb insuficiència renal crònica estadi IIIb (G3b), que correspon a un filtrat glomerular entre 44-30 ml/min/1.73m^2. *Chronic Kidney Disease* (CKD) correspon a Insuficiència Renal Crònica (IRC) en català, i GFR a filtrat glomerular.

Estadis de la insuficiència renal aguda (IRA) segons la classificació de KDIGO

Table 2 | Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

Font de la imatge (4). S'equipara la LRA-PC a la insuficiència renal aguda (IRA), estadi 1 de la classificació de KDIGO. *Acute Kidney Insuficiency* (AKI) correspon a Insuficiència Renal Aguda (IRA) en català.

ENUMERACIÓ D'ARTICLES QUE COMPOSEN LA TESI DOCTORAL

El document d'aquesta tesi està estructurat seguint les directrius de **TESI EN FORMAT DE COMPENDI D'ARTICLES.**

PRIMER ARTICLE

El primer article que composa aquesta tesi ha estat publicat el gener del 2021 a la revista *European Journal of Radiology*, revista indexada a la base de dades del *Journal Citation Reports* (JCR®) de la *Web of Knowledge*, a la categoria de *Radiology, Nuclear Medicine & Medical Imaging* en el segon quartil (Q2), amb un factor d'impacte el 2020 de 3.528.

La referència complerta es detalla a continuació (5):

Sebastià C, Páez-Carpio A, Guillen E, Paño B, Garcia-Cinca D, Poch E, Oleaga L, Nicolau C. Oral hydration compared to intravenous hydration in the prevention of post-contrast acute kidney injury in patients with chronic kidney disease stage IIIb: A phase III non-inferiority study (NICIR study). Eur J Radiol. 2021 Mar;136:109509. doi: 10.1016/j.ejrad.2020.109509. Epub 2021 Jan 14. PMID: 33516141.

SEGON ARTICLE

El segon article que composa aquesta tesi ha estat publicat a la revista *Supportive Care in Oncology* l'octubre del 2021. Aquesta revista està indexada a la base de dades del *Journal Citation Reports* (JCR®) de la *Web of Knowledge*, a la categoria de *Health Care, Sciences & Services*, en el segon quartil (Q2), amb un factor d'impacte el 2020 de 3.603 (6).

Sebastià C, Páez-Carpio A, Guillen E, Paño B, Arnaiz JA, de Francisco AJL, Nicolau C, Oleaga L. Oral hydration as a safe prophylactic measure to prevent post-contrast acute kidney injury in oncologic patients with chronic kidney disease (IIIb) referred for contrast-enhanced computed tomography: subanalysis of the oncological group of the NICIR study. *Support Care Cancer* (2021). https://doi.org/10.1007/s00520-021-06561-7

1

RESUM DE LA TESI DOCTORAL

1. RESUM DE LA TESI DOCTORAL

Introducció

La lesió renal aguda postcontrast (LRA-PC) es defineix com un increment de la creatinina sèrica (Cr) ≥ 0,3mg/dl (26,5µmol/l) o ≥ 1,5 vegades comparada amb el valor basal de la Cr que apareix entre les 48-72 hores després de l'administració intravascular del contrast iodat. L'existència d'insuficiència renal crònica (IRC) es considera el factor de risc principal associat a l'aparició de la LRA-PC. La hidratació per via intravenosa (i.v.) és en l'actualitat l'única forma de profilaxi efectiva de la LRA-PC.

Hipòtesi

La hidratació per via oral no és inferior a la hidratació per via i.v. com a mesura profilàctica de la LRA-PC en pacients amb IRC estadi IIIb als que se'ls hi realitzi una tomografia computaritzada (TC) administrant contrast iodat i.v.

Objectius

L'objectiu principal d'aquesta tesi és l'avaluació de forma prospectiva i randomitzada de la no inferioritat de la hidratació per via oral comparada amb la hidratació per via i.v. en la prevenció de la LRA-PC en pacients amb IRC estadi IIIb referits per una TC amb contrast iodat.

Els objectius secundaris són: 1) l'anàlisi de la necessitat d'hemodiàlisi durant el mes posterior a la realització de la TC amb contrast iodat en el grup d'hidratació oral i en el d'hidratació i.v.; 2) l'anàlisi de la reversibilitat de la LRA-PC 15 dies després de la realització de la TC amb contrast iodat en els dos grups; 3) l'avaluació de la seguretat en ambdós grups d'hidratació; 4) l'avaluació de la no inferioritat de la hidratació via oral versus la hidratació via i.v. en la prevenció de la LRA-PC en el subgrup de pacients oncològics.

Material i mètodes

S'ha realitzat un assaig clínic unicèntric, prospectiu, de distribució aleatòria, no emmascarat, amb dos grups paral·lels, de no inferioritat, l'estudi NICIR. Els pacients s'han randomitzat assignant-se 1:1 per rebre una pauta de profilaxi contra la LRA-PC sigui amb hidratació via oral: 500 ml d'aigua dues hores abans i 2000 ml durant les 24 hores després de l'administració de contrast iodat o amb hidratació i.v.; bicarbonat sòdic (166mmol/l) 3 ml/kg/h començant una hora abans i bicarbonat sòdic (166mmol/l) 1 ml/kg/h durant l'hora posterior a la TC amb contrast iodat.

Retrospectivament, també hem analitzat aquesta no inferioritat de la hidratació oral respecte a la hidratació i.v. en el subgrup de pacients oncològics, que suposen el 74% dels pacients de l'estudi NICIR.

Resultats

Dels 228 pacients que es van randomitzar entre el gener del 2018 fins al gener del 2019, 114 van rebre hidratació i.v. i 114 hidratació oral i van ser avaluables. No es van trobar diferències significatives en els factors de risc i les característiques clíniques associades entre les dues branques de l'estudi (p=0.13->0.95). La ràtio de LRA-PC va ser del 4.4% (95%CI: 1.4-9.9%) a la branca d'hidratació oral i del 5.3% (95%CI: 2.0-11.1%) a la branca d'hidratació i.v. La ràtio de LRA-PC no reversible va ser de 1.8% (95%CI: 0.2-6.2%) a les dues branques. Cap pacient va requerir diàlisi durant el mes posterior a la TC i no hi va haver cap efecte advers relatiu al règim d'hidratació. Dels 174 pacients inclosos en la subanàlisi retrospectiva dels pacients oncològics, 82 van rebre hidratació oral i 92 i.v. La ràtio de LRA-PC va ser del 3.7% a la branca d'hidratació oral i del 5.4% en la i.v. La LRA-PC persistent va ser de 1,8% a la branca oral i de 3.3% a la i.v.

Conclusions

L'estudi NICIR demostra que la hidratació per via oral no és inferior a la hidratació per via i.v. com a mesura profilàctica de la LRA-PC en pacients amb IRC estadi IIIb als que se'ls hi realitza una TC amb contrast iodat. Aquesta hipòtesi també queda demostrada al subgrup de pacients oncològics, que aquest estudi ha avaluat específicament de manera retrospectiva.

2

INTRODUCCIÓ

2. INTRODUCCIÓ

2.1. Contrasts iodats: tipus i vies d'administració

Els mitjans de contrast que s'utilitzen en proves radiològiques de raigs X, com la tomografia computaritzada (TC), són substàncies que es fan servir amb finalitats diagnòstiques per la seva capacitat d'absorbir raigs X en major o menor grau que els teixits tous adjacents. Es classifiquen, respectivament, en contrasts positius o negatius. Aquesta característica dels contrasts permet obtenir la representació visual de determinades estructures i òrgans, així com de cavitats i de processos funcionals de l'organisme. Els contrasts radiològics positius poden ser contrasts iodats o de bari i els contrastes radiològics negatius són l'aigua i l'aire.

Els mitjans de contrast iodats són sals de iode que bàsicament es divideixen en:

- iònics (disposen d'un radical carboxílic) i no iònics (disposen d'un radical hidroxílic).
- hipoosmolars, isoosmolars o hiperosmolars.
- monomèrics o dimèrics, segons tinguin un o dos nuclis benzoics.

A la figura 1 veiem un resum dels més emprats:

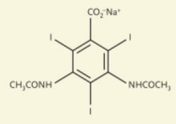
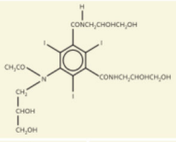
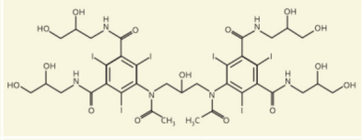
	High Osmolality	Low Osmolality		Iso-osmolality
Molecular Structure				
	Ionic monomer	Ionic dimer	Nonionic monomer	Nonionic dimer
Generic Name (mg contrast/ml)	Diatrizoate meglumine and diatrizoate sodium (760)	Ioxaglate meglumine and ioxaglate sodium (589)	Iopamidol (408) Iopamidol (510) Iopamidol (612) Iopamidol (755)	Iodixanol (550) Iodixanol (652)
Iodine Concentration (mg/ml)	370	320	200–370	270–320
Osmolality (mOsm/kg H_2O)	1551	~600	413–796	290
Viscosity (mPa·sec at 37°C)	10.5	7.5	2.0–9.4	6.3–11.8

Figure 1. Classification of Available Contrast Agents.
Contrast agents are classified according to osmolality. Examples of molecular structures and specific agents are shown, and characteristics are described according to the American College of Radiology's *Manual on Contrast Media*.[8]

Figura 1: Classificació dels contrasts iodats (7).

Els primers contrasts iodats eren **contrasts iodats iònics** majoritàriament **hiperosmolars** envers el plasma. Aquests contrasts presentaven molts efectes secundaris i avui en dia ja no s'utilitzen en la pràctica clínica. Molts dels efectes secundaris que en l'actualitat s'atribueixen als contrasts iodats són els que presentaven aquests primers contrasts iodats iònics hiperosmolars, que estan fora del mercat fa dècades.

En l'actualitat disposem de **contrasts iodats no iònics,** que es classifiquen en **isoosmolars** (respecte al plasma) i **hipoosmolars** (respecte als hiperosmolars). Els contrasts denominats hipoosmolars s'anomenen així perquè tenen una osmolaritat molt menor que la que tenien els antics contrast iodats iònics hiperosmolars (610-690 mOsmol/kg d'aigua dels contrasts anomenats hipoosmolars versus 1710 mOsmol/kg d'aigua dels contrasts hiperosmolars), tot i que la seva osmolaritat és major a la del plasma (290 mOsmol/kg d'aigua). És important conèixer aquest detall perquè pot portar a interpretacions errònies i —com explicarem a la discussió— ha estat motiu de debat en la comunitat científica (8).

Les vies d'administració dels contrasts iodats són principalment dues: la via arterial i la via intravenosa (i.v.). El Contrast Media Safety Committee (CMSC) de la European Society of Urogenital Radiology (ESUR), en l'última actualització de les seves guies (guia ESUR 10.0 del 2019), diferencia l'administració de contrast intraarterial en dos tipus: la injecció de primer pas i la de segon pas. En la injecció arterial de primer pas el contrast arriba sense diluir al ronyó —és a dir, sense que hagi fet tot el cicle cardíac— i en la injecció arterial de segon pas el contrast arriba diluït al ronyó. A tall d'exemple, si el contrast s'injecta al ventricle esquerre, a l'aorta toràcica, a l'aorta abdominal per sobre de les artèries renals o directament a les artèries renals seria una injecció arterial de contrast de primer pas; si s'injecta per sota de les artèries renals es consideraria una injecció arterial de contrast de segon pas (2). Tot i que aquesta diferenciació de contrast diluït/no diluït té lògica a nivell teòric per tal d'explicar un diferent nivell de nefrotoxicitat del contrast iodat no ha estat provada a nivell experimental.

El motiu d'aquesta tesi és l'estudi de la nefrotoxicitat del contrast iodat injectat per via i.v. En aquesta introducció ens basarem en l'evidència científica publicada específicament pel contrast administrat per aquesta via, la i.v.

2.2. Contrasts iodats i nefrotoxicitat

El 1956, Bartels et al. van publicar a l'*Acta Medica Scandinavica* el primer cas que relacionava l'administració de contrast iodat amb l'empitjorament de la funció renal, anúria, en un pacient que presentava un mieloma múltiple (MM) (figura 2) (9). Per aquesta raó, durant molts anys el MM, *per se*, és considerat un factor de risc per a la insuficiència renal aguda (IRA) associada a l'administració de contrast iodat, quan el que realment constituïa un factor de risc era la insuficiència renal crònica (IRC) que sovint s'associa al MM. Actualment el MM ja no es considera un factor de risc específic per a la nefropatia associada al contrast iodat.

Acta Med Scand. 1954;150(4):297-302.

Acute anuria following intravenous pyelography in a patient with myelomatosis.

BARTELS ED, BRUN GC, GAMMELTOFT A, GJØRUP PA.

PMID: 13217726 [PubMed - OLDMEDLINE]

Figura 2. Primer article on es publica un cas que relaciona l'administració de contrast iodat i l'empitjorament de la funció renal (9).

El 1980 Mudge va publicar a la revista *Kidney International* la primera sèrie de 13 pacients en que relacionava l'administració de contrast iodat intravascular per a la realització de proves radiològiques amb l'empitjorament de la funció renal (figura 3) (10).

Kidney International, Vol. 18 (1980), pp. 540–552

Nephrotoxicity of urographic radiocontrast drugs

GILBERT H. MUDGE

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Figura 3. Primera sèrie publicada associant l'administració de contrast iodat amb l'aparició d'insuficiència renal aguda (10).

A partir dels anys 80 la literatura que relaciona els contrasts iodats amb l'empitjorament de la funció renal va créixer exponencialment. En general, les publicacions dels anys 80 i 90 són retrospectives, sense casos control i molt heterogènies, barrejant diferents contrasts (iònics i no iònics), diferents dosis de contrast, diferents formes d'administració del contrast (arterial i i.v) i amb pacients amb molt diferents nivells de comorbiditat segons les sèries. Aquesta marcada heterogeneïtat entre les sèries publicades dificulta que es pugui establir una prevalença clara d'aquesta entitat, que és mou en un rang amplíssim que va del 3.3% al 10.5% i que pot arribar fins el 50% en pacients d'alt risc, segons les sèries (11). Els contrasts iodats es consideren també, històricament, com la tercera causa d'IRA en pacients hospitalitzats després de la hipoperfusió renal i les medicacions nefrotòxiques (11).

En paral·lel , a partir de la dècada dels 80, els clínics —i especialment els radiòlegs—, vam passar de la total ignorància sobre la possible nefrotoxicitat del contrast iodat (injectant dosis de contrast molt altes i de forma repetida en els estudis radiològics, especialment en els d'angioradiologia), fins a l'extrem contrari. Per la por a lesionar la funció renal es negava el contrast iodat a pacients que ho necessitaven per tenir un diagnòstic acurat i ràpid de la seva malaltia, cosa que era de vital importància pel correcte maneig del pacient.

El 1999, l'ESUR va començar a anomenar aquesta relació contrast iodat/nefrotoxicitat com a nefropatia induïda per contrast (NIC), que es defineix com l'empitjorament de la funció renal que apareix durant els tres dies posteriors a l'administració intravascular de un mitjà de contrast iodat, en absència d'una etiologia alternativa, amb un increment del valor de la creatinina (Cr) major del 25% o 44,5µmol/l (0,5 mg/dl) (1).

El 2017, la NIC va passar a denominar-se lesió renal aguda postcontrast (LRA-PC), en anglès *post-contrast acute kidney injury* (PC-AKI), que es defineix com un increment de la Cr ≥ 0,3mg/dl (26,5µmol/l) o ≥ 1,5 vegades comparada amb el valor basal de la Cr que apareix entre les 48-72 hores després de l'administració intravascular del contrast iodat, en absència d'una etiologia alternativa (12).

Aquest canvi de nomenclatura de NIC a LRA-PC, que bàsicament representa el canvi de l'augment de la Cr de 0,5mg/dl a 0,3mg/dl en la definició, ha estat molt celebrat pels nefròlegs considerant que no tenia cap sentit que totes les insuficiències renals agudes grau I de la classificació KDIGO es definissin com un augment de 0,3mg/dl de la Cr i no així la NIC (4). A partir d'aquest moment, en el text d'aquesta tesi, i per evitar confusions, ens referirem sempre a l'associació entre nefrotoxicitat i contrast iodat com a LRA-PC, independentment de la definició que s'hagi fet servir en els diferents estudis referenciats.

En la literatura anglosaxona trobem encara dos termes més per a referir-se a la relació dels contrasts iodats amb l'empitjorament de la funció renal que també poden crear confusió. El primer és el *contrast-associated acute kidney injury* (CA-AKI) que es correspon a la LRA-PC/PC-AKI i el segon és el *contrast-induced acute kidney injury* (CI-AKI) que, a l'igual que la NIC, indiquen causalitat del contrast iodat en qualsevol canvi de la funció renal que es produeixi després d'una prova radiològica. Actualment aquesta última nomenclatura, CI-AKI, també es desaconsella pel mateix motiu que s'ha

deixat d'utilitzar la nomenclatura NIC, i és per no inferir causalitat de dos fenòmens consecutius que serien la injecció de contrast iodat i l'elevació de la creatinina i evitar el que es coneix en llatí com *post hoc, ergo propter hoc*, que ha estat una de les causes principals de la sobredimensió de la prevalença de la LRA-PC (11,12).

La fisiopatologia de la LRA-PC es basa en estudis animals, perquè per motius ètics no poden realitzar-se biòpsies seriades abans i després de l'administració de contrast iodat als pacients. La patogènesi de la LRA-PC està relacionada amb el dany directe causat pel contrast iodat a les cèl·lules epitelials i endotelials renals seguit d'inflamació, estrès oxidatiu, augment de la càrrega osmòtica i, finalment, hipoperfusió i hipòxia. La patogènia de la LRA-PC està esquematitzada a la figura 4 (11).

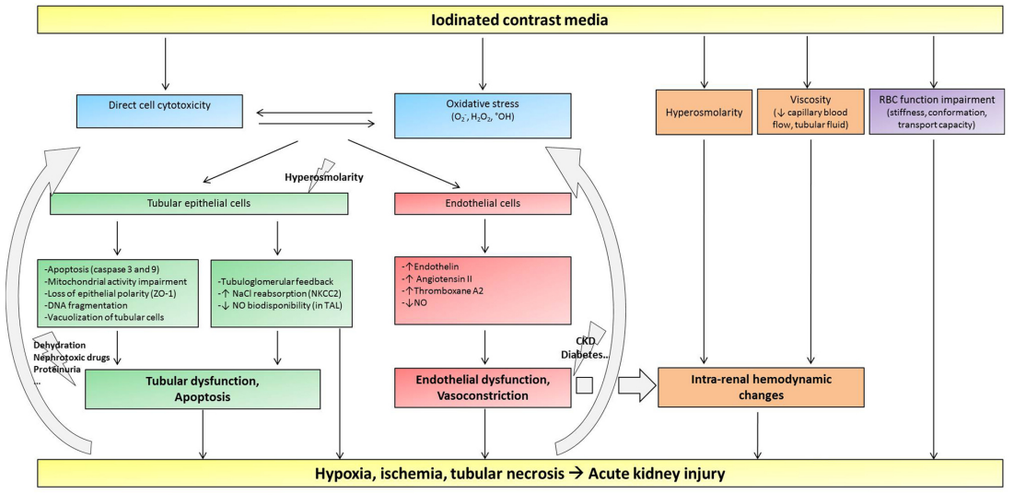

Figura 4. Esquema de la fisiopatologia del dany renal produït per l'administració de contrast iodat, extret de (11).

La por a la LRA-PC, tal com ja hem comentat abans, va fer que progressivament clínics i radiòlegs fóssim cada cop més restrictius a l'hora d'indicar l'administració de contrast iodat en pacients amb IRC, fins que el 2008 Newhouse et al. van publicar un article en el que es qüestionava la causalitat del contrast iodat en les variacions de la Cr. Newhouse et al. van demostrar que les variacions fisiològiques de la Cr, *per se*, poden produir oscil·lacions iguals o superiors a les que defineixen la LRA-PC sense que el pacient hagi rebut contrast iodat (13). A partir d'aquest moment es va començar a

parlar de que la LRA-PC no era sinó una «creatinopatia», es a dir, es considerava com una malaltia el que tan sols seria una variant de la normalitat (veure figura 5).

Genitourinary Imaging • Original Research

Frequency of Serum Creatinine Changes in the Absence of Iodinated Contrast Material: Implications for Studies of Contrast Nephrotoxicity

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Keywords: contrast material, iodinated contrast material, nephropathy, nephrotoxicity, renal failure

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TABLE 1: Effect of Initial Creatinine Level on Frequency of Change at Various Thresholds

Threshold Increase	0.6–1.2 mg/dL (19,123 pacientes)	1.3–2.0 mg/dL (6,221 pacientes)	2.1–3.0 mg/dL (1,974 pacientes)	> 3.0 mg/dL (2,292 pacientes)
25%	27%	20%	18%	14%
33%	19%	5%	8%	6%
50%	14%	10%	9%	6%
0.2 mg/dL	33%	35%	37%	46%
0.4 mg/dL	13%	21%	26%	38%
0.6 mg/dL	7%	14%	19%	31%
1.0 mg/dL	3%	7%	11%	22%

Note—Percentages listed indicate cumulative fraction of patients reaching threshold on any day during 5-day period.

Figura 5. Gràfica de l'article de Newhouse (13) on es demostra que les variacions fisiològiques de la creatinina remarcades en el quadrat lila poden presentar valors similars a les de la definició de la LRA-PC i que aquesta variabilitat intrínseca és més marcada com pitjor sigui la funció renal del pacient (rodones taronja).

La teoria de Newhouse va quedar reforçada per l'article que van publicar McDonald et al. el 2013 (14). Aquest grup, per compensar l'absència d'un grup control que per problemes ètics no es podia tenir (no podem privar de l'administració de contrast iodat en proves radiològiques a un grup de pacients sabent que fent-ho dificultem el seu correcte diagnòstic i seguiment) va utilitzar el mètode d'emparellament de mostres anomenat *Propensity Score Matching*. Newhouse et al., avaluant 12.500 pacients, va demostrar que les variacions de la Cr en pacients amb similars característiques clíniques després de realitzar una TC amb o sense contrast iodat eren equiparables. En aquest article també comparava aquestes oscil·lacions de la Cr en un mateix pacient quan se li realitzava un estudi amb TC amb contrast i un sense i s'arribava a la mateixa conclusió (figura 6).

ORIGINAL RESEARCH ■ CONTRAST MEDIA

Intravenous Contrast Material–induced Nephropathy: Causal or Coincident Phenomenon?[1]

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John P. Bida, PhD
Rickey E. Carter, PhD
Chad J. Fleming, MD
Sanjay Misra, MD
Eric E. Williamson, MD
David F. Kallmes, MD

Purpose: To determine the causal association and effect of intravenous iodinated contrast material exposure on the incidence of acute kidney injury (AKI), also known as contrast material–induced nephropathy (CIN).

Materials and Methods: This retrospective study was approved by an institutional review board and was HIPAA compliant. Informed consent was waived. All contrast material–enhanced (contrast

Radiology

Figure 2

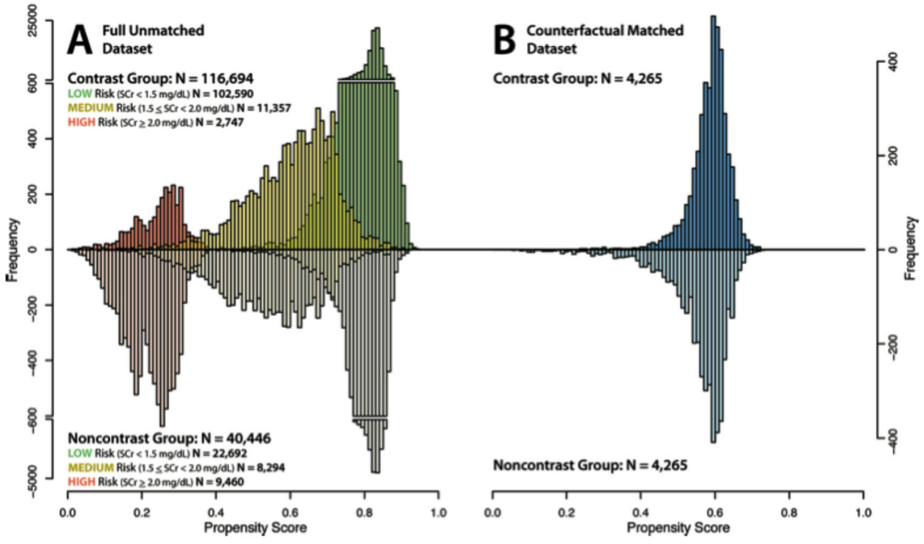

Figure 2: Chart shows distribution of propensity scores in study population. Patients who underwent contrast-enhanced CT scan (contrast group) are shown above the x-axis and patients who underwent unenhanced CT scan (noncontrast group) are shown below the x-axis. *A*, Distribution of the full unadjusted data set (n = 157 140) and low-, medium-, and high-risk subgroups. *B*, Distribution of the subset of scans included in the counterfactual analysis (n = 8530).

Figura 6. Capçalera i gràfica de l'article de McDonald (14). A l'esquema veiem les variacions de la creatinina en TCs amb contrast (en positiu) i amb TCs sense contrast (en negatiu) en pacients diferents amb similars característiques clíniques (esquerra) i en el mateix pacient (dreta). Les gràfiques demostren una variabilitat de la creatinina similar en TCs amb contrast i sense contrast.

Destaquem també l'article de Davenport et al. del 2013 (15). En aquest article els autors van concloure que l'administració de contrast iodat és un factor de risc independent per la LRA-PC en pacients amb un FG menor de 30ml/min/1.73m^2, però que no ho és en FG superiors (figura 7).

Radiology

Contrast Material–induced Nephrotoxicity and Intravenous Low-Osmolality Iodinated Contrast Material: Risk Stratification by Using Estimated Glomerular Filtration Rate[1]

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Richard H. Cohan, MD
Jonathan R. Dillman, MD
James D. Myles, PhD

Purpose: To determine the effect of intravenous (IV) low-osmolality iodinated contrast material (LOCM) on the development of post-computed tomography (CT) acute kidney injury (AKI), stratified by pre-CT estimated glomerular filtration rate (eGFR), in patients with stable renal function.

ORIGINAL RESEARCH ■ CONTRAST MEDIA

Figura 7. En aquest article Davenport et. al van demostrar que l'administració de contrast és un factor de risc independent per a l'aparició de la LRA-PC en pacients amb un FG menor de 30 ml/min/1.73m^2 però no si el FG és superior (15).

A partir de la publicació d'aquests articles la comunitat radiològica es va començar a qüestionar si realment la por històrica a realitzar estudis amb contrast en pacients amb IRC tenia base científica, i fins i tot si la LRA-PC existia. A tall d'exemple veiem la capçalera d'un dels múltiples editorials que posen en dubte l'existència de la LRA-PC a la figura 8 (16).

Contrast-Induced Nephropathy: Contrast Material Not Required?

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James H. Ellis[2]

OBJECTIVE. This commentary deals with the study by Newhouse and colleagues in this issue of the *AJR* discussing the implications of a lack of a control group in previously published studies on contrast-induced nephropathy (CIN).

CONCLUSION. Until more rigorous studies including an appropriate control group address the issue of CIN, our understanding of the actual risk of CIN when administering IV contrast media is limited.

Figura 8. En aquesta imatge incloem la capçalera d'un dels múltiples editorials i comentaris que apareixen a la literatura després del qüestionament de l'alta prevalença i fins i tot de l'existència de la LRA-PC (16).

Per últim, però no per això menys important, s'ha de tenir en compte que l'empitjorament de la funció renal després de realitzar una prova radiològica amb contrast iodat és en la majoria dels casos reversible: és a dir, que la Cr torna als valors d'abans de la prova en menys de 15 dies i, a més a més, la necessitat d'hemodiàlisi si el pacient presenta una LRA-PC és pràcticament inexistent. L'empitjorament de la funció renal de manera irreversible o persistent té una prevalença molt inferior a les xifres diagnòstiques de la LRA-PC. Molts nefròlegs plantegen que l'administració repetida de contrast iodat pot provocar una lesió renal subclínica acumulativa que no es pot quantificar perquè queda emmascarada per la capacitat renal de mantenir-se estable gràcies a la reserva funcional renal, però malauradament això no s'ha pogut provar. En el futur esperem que empitjoraments de la funció renal subclíniques emmascarades per la reserva funcional renal puguin valorar-se amb nous biomarcadors clínics (17).

2.3. Factors de risc associats a la lesió renal aguda postcontrast

Múltiples factors de risc s'han associat històricament a la LRA-PC i es divideixen bàsicament en dos grups: els associats al pacient i els associats al procediment.

La preexistència d'IRC es considera el factor de risc principal associat al pacient per desenvolupar una LRA-PC, a més de la insuficiència renal aguda (IRA), l'estat crític del pacient i la deshidratació o la depleció de volum (2). Clàssicament s'han considerat factors de risc associats al pacient la diabetis, la insuficiència cardíaca, la hipertensió, la hipotensió, la cirrosi hepàtica, la malaltia cardiovascular, l'anèmia, el sexe femení, ser major de 75 anys, el càncer, la inflamació, el MM, tenir un sol ronyó, el trasplantament hepàtic, renal i/o pancreàtic, la hiperuricèmia, i les medicacions nefrotòxiques, entre d'altres.

Actualment, els factors que hem detallat al paràgraf anterior no es consideren de risc específic per desenvolupar la LRA-PC, sinó que en realitat serien factors de risc per desenvolupar una IRC i una IRA de qualsevol etiologia, per la qual cosa el CMSC de la ESUR, a les seves guies 10.0, els han eliminat com a factors de risc específics per la LRA-PC (2).

Com veurem més endavant, el fet de deixar de considerar factors de risc tots els detallats anteriorment no ha estat acceptat per totes les societats radiològiques i tampoc per les societats cardiològiques, nefrològiques i oncològiques (18-20). En l'apartat de les mesures profilàctiques de la LRA-PC parlarem de les conseqüències clíniques de no tenir en compte aquests factors de risc i com aquesta tesi busca una solució per protegir tots aquests pacients amb una funció renal especialment làbil i, específicament, als pacients oncològics (21).

Els factors de risc associats al procediment són els relacionats amb la injecció del contrast i inclouen dosis altes de contrast, injecció via arterial, us de contrasts hiperosmolars (actualment, repetim, fora del mercat), injeccions múltiples de contrast en un període inferior a 48-72 hores i la realització de proves d'intervencionisme cardiovascular (2).

Clàssicament s'ha associat la injecció de contrast per via arterial a una major prevalença de LRA-PC. Aquest fet actualment també està en qüestió (22). Existeix també una prolífica literatura científica sobre els suposats avantatges dels contrasts isoosmolars sobre els hipoosmolars en la prevenció de la LRA-PC tot i que les darreres metaanàlisis no troben diferencies significatives entre aquests dos tipus de contrasts quan s'administren per via i.v. Les guies de la ESUR i la guia de consens entre el American College of Radiology (ACR) i la National Kidney Fundation tampoc fan diferències entre l'administració de contrast isoosmolar o hipoosmolar (12,23).

Menció especial mereix la metformina. Fins fa poc les guies requerien discontinuar la metformina quan s'administrés contrast iodat pel risc a provocar una acidosi làctica. Actualment no es considera necessari retirar la metformina si el pacient té un FG major de 30 ml/min/1.73m^2 i està ben hidratat. Recordem que amb FG menors de 30 ml/min/1.73m^2 la metformina està formalment contraindicada, per la qual cosa pràcticament no ens trobarem en la pràctica diària amb pacients als que se'ls hi hagi de retirar aquesta medicació. Per altra banda és important recalcar que la metformina no és nefrotòxica, es a dir que no es un factor de risc per la LRA-PC (23).

2.4. Profilaxi de la lesió renal aguda postcontrast

A partir dels anys 80, quan que es relacionava l'administració de contrast iodat amb l'empitjorament de la funció renal, la comunitat mèdica començava a ser cada cop més prudent a l'hora d'administrar els contrasts iodats i van començar a aparèixer a la literatura científica múltiples pautes de profilaxi de la LRA-PC basades en la hidratació i.v. Es publicava també la utilitat de múltiples medicacions nefroprotectores, tot i que només la N-acetilcisteina va arribar a aconsellar-se en les guies clíniques. Posteriorment les metaanàlisis que avaluaven l'efectivitat de la N-acetilcisteina no van aconseguir demostrar la superioritat d'aquest fàrmac associant-lo a la hidratació i.v. en comparació amb l'efectivitat de la hidratació i.v. sola com a forma de profilaxi de la LRA-PC (24). Després de la publicació d'aquestes metaànalisis va deixar de recomanar-se en les guies clíniques de referència de l'American College of Radiology (ACR) del 2013 i de la ESUR del 2014 (ESUR 8.1) (25,26). La hidratació per via i.v. es considera des del 2013 l'única forma de profilaxi efectiva de la LRA-PC. Fins a dia d'avui cap medicació ha demostrat ser realment útil com a forma de profilaxi i no s'ha incorporat cap altre tractament farmacològic a les guies clíniques. Les pautes d'hidratació i.v. són molt variades i canvien segons la guia clínica consultada. Fins el 2019, el llindar a partir del qual es considerava indicada la profilaxi de la LRA-PC era tenir un FG menor de 45ml/min/1.73m^2 en la pràctica totalitat de les guies clíniques radiològiques.

Els assajos AMACING i Kompas, dos estudis prospectius randomitzats multicèntrics de no inferioritat publicats recentment qüestionen la necessitat d'hidratar com a forma de profilaxi de la LRA-PC als pacients amb IRC grau IIIb de la classificació KDIGO; és a dir, la forquilla de FG que va entre els 45 i 30ml/min/1.73m^2 (27,28). Aquests dos estudis han motivat que l'ACR i el CMSC de l'ESUR, entre altres societats radiològiques, hagin baixat el llindar per indicar el tractament profilàctic d'hidratació abans de l'administració i.v. de contrast iodat d'un FG de 45 ml/min/1.73m^2 a un FG de 30ml/min/1.73m^2. Tanmateix, aquestes recomanacions no han estan acceptades per tota la comunitat radiològica, que en alguns casos segueixen aconsellant que es deixi el llindar de profilaxi de la LRA-PC en un FG de 45mL/min/1.73m^2, tal com estava establert en les guies prèvies al 2019 (17,18). Per altra banda, la comunitat nefrològica i oncològica veu insuficient l'evidència científica per baixar aquest llindar i recomana una actitud més prudent i defensa que es molt aviat per declarar la inefectivitat o la no necessitat de la hidratació per prevenir la LRA-PC en aquest grup de pacients i també recomanen deixar el llindar de profilaxi en un FG de 45mL/min/1.73m^2 o menor. Fins i tot en algunes guies aconsellen hidratar si el FG es menor de 60mL/min/1.73m^2 (8).

Com hem assenyalat abans, les pautes d'hidratació i.v. són molt variades i seria farragós enumerar-les totes en aquesta introducció. Només direm que actualment l'ESUR recomana pautes d'hidratació curtes i la ACR i les societats nefrològiques i cardiològiques més llargues, amb resultats similars. Aquestes guies deixen oberta la porta a la hidratació per via oral però constaten que no hi ha prou evidència científica per incloure-la com a recomanació a les guies clíniques (12,23). L'objectiu principal d'aquesta tesi és aportar aquesta evidència científica.

Per últim, cal dir que existeix controvèrsia sobre si és millor realitzar la hidratació profilàctica intravenosa amb sèrum fisiològic o amb bicarbonat. Tot i que hi ha moltes més publicacions que avalen l'eficàcia del bicarbonat per damunt del sèrum fisiològic, el consens científic és que els dos tipus d'hidratació es poden considerar igual d'efectives (29).

2.5. La nostra experiència en la profilaxi de la lesió renal aguda postcontrast

Com explicàvem en el paràgraf anterior, les pautes d'hidratació i.v. com a mesura de profilaxi de la LRA-PC són molt heterogènies i variables d'una guia a una altra. Les primeres pautes que van aparèixer en les guies clíniques eren molt llargues, començant fins i tot 24 hores abans de la prova amb contrast i fins a 24 hores després. Aquestes pautes estaven pensades per a malalts ingressats —i especialment per a malalts cardiòpates— a fi d'evitar una sobrecàrrega hídrica, però la seva implementació en la pràctica clínica en pacients ambulatoris era totalment inviable.

A l'Hospital Clínic, per poder universalitzar la hidratació profilàctica, i amb la col·laboració inestimable del Dr. Esteban Poch del servei de Nefrologia, el 2010 es va escriure la primera guia clínica intrahospitalària per a prevenir la LRA-PC. S'utilitzava una pauta d'hidratació curta pels pacients amb FG entre 45 i 30ml/min/1.73m^2 de dues hores de durada consistent en bicarbonat sòdic (166mmol/l) o sèrum fisiològic 3 ml/

kg/h començant una hora abans de la TC amb contrast i bicarbonat sòdic (166mmol/l) o sèrum fisiològic 1 ml/kg/h durant l'hora després de la prova, —anomenada pauta 1h/1h— i una pauta més llarga pels pacients amb FG menor de 30ml/min/1.73m^2, similar a la anterior però amb una durada de sis hores després de l'administració de contrast, anomenada pauta 1h/6h. En aquesta guia intrahospitalària també s'indicava la hidratació oral quan la hidratació i.v. no era possible, amb una pauta que consistia en beure 500 ml d'aigua dues hores abans de la TC amb contrast i 2000 ml durant les 24 hores posteriors a la prova. Aquestes pautes que acabem de descriure, amb petites variacions, s'han publicat a la literatura i mostren resultats equivalents a pautes d'hidratació més llargues (30,31).

L'any 2018 vam presentar els resultats de l'aplicació d'aquestes pautes al nostre hospital al Congrés Nacional de la Societat Española de Radiologia. La prevalença de LRA-PC a la nostra sèrie era del 2.3%, essent irreversible (persistent) tan sols en el 0.38% dels casos i sense que cap pacient requerís diàlisi. És important remarcar que en la nostra sèrie a 170 dels 780 pacients se'ls hi va fer hidratació profilàctica per via oral, i cap d'ells va presentar LRA-PC. A la figura 9 es pot veure el resum de les característiques de la nostra sèrie i els resultats de l'aplicació d'aquestes pautes d'hidratació del 2013 al 2017 a l'Hospital Clínic.

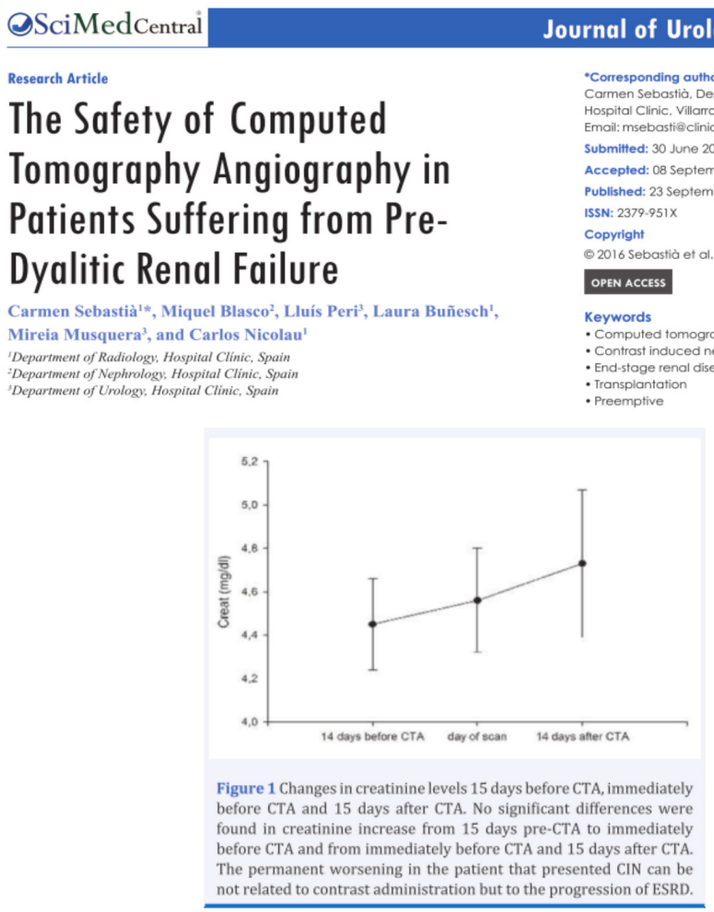
Tamaño muestral (n)	**780**
Edad media (años, rango)	68 (61-86)
Sexo (hombre/mujer)	432/349
FG (mL7min)	
45-30	630
30-15	150
Hidratación endovenosa (1h/1h)	610
Hidratación oral (500mL/2000mL)	170
Tamaño muestral (n)	**25**
Aumento creatinina 0.5mg/dl	25/780 (3.2%)
Hidratación ev (1h/1h)	25
Hidratación oral (500ml/2000ml)	0
Aumento creatininia 0.5mg/dl	25
FG entre 30-45ml/min	6
FG menor a 30ml/min	19
Aumento de creatinina atribuible a otras causas:	7/780 (0.9%)
Progresión hidronefrosis	5
Fallo multiorgánico	1
Quimioterapia	1
NIC	18/780 (2.3%)
Reversible	15 (1.92%)
Irreversible	3 (0.38%)
Diálisis	0

NIC: 2.3%
Irreversible 0.38%
Ningún paciente diálisis

Figura 9. Del 2013 al 2017 780 pacients amb FG menor de 45ml/min/1.73m^2 van rebre hidratació profilàctica per prevenir la LRA-PC. Les característiques de la sèrie i els resultats es resumeixen a la taula de la dreta.

Per altra banda, essent l'Hospital Clínic un centre de referència pel trasplantament renal —i específicament pel trasplantament de donant viu de ronyó— ens trobem en la necessitat de fer mapes vasculars acurats pretrasplantament a molts receptors que només podem aconseguir realitzant un angio-TC amb contrast iodat, cosa que no és un problema si el pacient està en hemodiàlisi però sí en el cas de que la prova s'hagi de realitzar a un pacient amb insuficiència renal preterminal o, si estant en diàlisi, presenta micció residual. Per aquesta raó realitzem un estudi prospectiu en aquest subgrup de pacients —candidats a ser receptors de donant viu renal amb insuficiència renal preterminal— als quals fem un estudi d'angio-TC amb contrast un mes abans de la data de trasplantament, realitzant en aquests casos la pauta habitual dels pacients amb un FG menor de 30ml/min/1.73m^2 de 1h/6h (bicarbonat sòdic (166mmol/l) o sèrum fisiològic, 3 ml/kg/h, començant una hora abans de la TC amb contrast i bicarbonat sòdic (166mmol/l) o sèrum fisiològic, 1 ml/kg/h durant les sis hores després de la prova).

En aquest estudi prospectiu de trenta-sis pacients només un mostra aparició de LRA-PC, irreversible. Però si mirem l'evolució de la creatinina en aquest pacient quinze dies abans de la realització de la TC amb contrast i quinze dies després, veiem que la corba d'empitjorament de la Cr no s'accelera, per la qual cosa no podem saber si aquest empitjorament de la funció renal és atribuïble a l'administració del contrast iodat o correspon únicament a l'evolució natural de la IRC terminal d'aquest pacient, com podem veure a la figura 10 (32).



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Research Article

The Safety of Computed Tomography Angiography in Patients Suffering from Pre-Dyalitic Renal Failure

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• Preemptive

Figure 1 Changes in creatinine levels 15 days before CTA, immediately before CTA and 15 days after CTA. No significant differences were found in creatinine increase from 15 days pre-CTA to immediately before CTA and from immediately before CTA and 15 days after CTA. The permanent worsening in the patient that presented CIN can be not related to contrast administration but to the progression of ESRD.

Figura 10. Capçalera de l'article en què es publica la sèrie dels pacients de l'Hospital Clínic amb IRC preterminal candidats a donació renal de viu als que se'ls hi fa una TC amb contrast un mes abans de la donació amb hidratació profilàctica i.v. (1h/6h). En aquesta figura també veiem la gràfica de l'evolució de la creatinina en el pacient que va presentar LRA-PC irreversible, que demostra que la corba d'empitjorament de la funció renal pre-TC no va ser diferent a la post-TC (32).

Basant-nos en els resultats dels nostres estudis arribem a dues conclusions importants. Per una banda, que la prevalença de la LRA-PC i —especialment de les formes irreversibles— és molt baixa, fins i tot en pacients amb IRC severes i/o terminals. Per altra banda, que tenim uns resultats excel·lents utilitzant la hidratació profilàctica per via oral. Aquests magnífics resultats que minimitzen la prevalència de la LRA-PC, i posen en valor l'eficàcia de la hidratació profilàctica per via oral ens porten a dissenyar l'assaig clínic que vol demostrar la no inferioritat de la hidratació oral envers la hidratació intravenosa i que esdevé l'objectiu principal d'aquesta tesi, l'estudi NICIR.

2.6. Pacients oncològics, particularitats

La TC amb contrast té un paper primordial en l'avaluació dels pacients amb càncer. La TC és essencial per caracteritzar i estadiar correctament la malaltia oncològica i per controlar evolutivament la resposta als tractaments oncològics i el risc de progressió o recaiguda durant el seguiment.

S'accepta àmpliament que els pacients oncològics tenen un major risc de desenvolupar IRA, que pot arribar al 17,5% a un any i fins al 27% als cinc anys després del diagnòstic del càncer (33). L'edat, el tipus de tumor, el tipus de tractament oncològic, l'ús de tractaments nefrotòxics, la deshidratació, les malalties renals preexistents i la nefrotoxicitat dels mitjans de contrast iodats, entre altres factors, poden influir en l'aparició d'IRA en aquests pacients (21).

Paral·lelament amb l'augment de l'esperança de vida, hi ha hagut un increment del nombre de pacients amb càncer, molts dels quals tenen múltiples factors de risc no oncològics que condueixen a l'aparició de la IRC (diabetis, hipertensió, malalties cardiovasculars i medicaments nefrotòxics, entre d'altres). A més, el mecanisme pel desenvolupament de l'IRC també pot dependre del tipus de tumor. Alguns, com ara els tumors malignes hematològics, poden causar IRA o IRC secundàriament a la sobreproducció i filtració de cadenes lleugeres tòxiques (que provoquen lesions tubulars), a la infiltració del parènquima renal o a la seva associació amb glomerulonefritis. Altres tumors, especialment els d'òrgans propers, poden envair directament les vies urinàries, provocant nefropatia obstructiva. A més, alguns pacients poden desenvolupar IRC després de sotmetre's a una nefrectomia parcial o total o a una

derivació urinària. Finalment, múltiples mecanismes fisiopatològics relacionats amb el propi càncer —com la depleció de volum, la sepsis o les síndromes paraneoplàsiques associades—, també poden provocar IRA (34).

La nefrotoxicitat pels tractaments específics del càncer és un altre aspecte que cal tenir en compte. La quimioteràpia convencional amb agents citotòxics pot causar toxicitat renal principalment per dany tubular o vascular. Els nous fàrmacs oncològics desenvolupats recentment bloquegen molècules específiques implicades en el creixement i progressió del tumor (teràpia dirigida), minimitzant així els efectes secundaris de la quimioteràpia convencional. No obstant això, aquestes teràpies dirigides també poden bloquejar mecanismes fisiològics de l'organisme i aquesta inhibició pot anar acompanyada d'efectes secundaris. En aquest sentit, amb aquestes noves teràpies dirigides s'han descrit diferents tipus de toxicitats que afecten diverses parts de la nefrona. Un dels trastorns més freqüents és la nefritis intersticial aguda. En resum, tant les teràpies convencionals com les dirigides poden afectar qualsevol segment de la nefrona (34).

A més de tots el potencials factors nefrotòxics associats al càncer que hem mencionat anteriorment, els pacients amb càncer necessiten proves d'imatges repetides al llarg del temps per controlar la malaltia, rebent així una exposició acumulativa important de contrast iodat (17)

2.7. Hidratació i dejú en proves radiològiques

El 2012, Lee et al. van publicar un article qüestionant la necessitat del dejuni abans de qualsevol estudi radiològic que es realitzi amb contrast iodat, observant una disminució de les molèsties dels pacients que no estaven sotmesos a dejuni programat abans de la prova (35). Lee et al. no van trobar cap cas de pneumònia per aspiració atribuïble a la ingestió de sòlids i líquids abans d'una TC amb contrast iodat. És possible que aquesta complicació fos específica de la injecció de contrast iodat iònic, ara exclosa de la pràctica clínica. A més, Barbosa et al. el 2016 van demostrar que el dejuni abans de la TC amb contrast augmenta la freqüència de nàusees i vòmits (36).

Barbosa et al. també van argumentar que el dejuni prolongat de líquids i sòlids que es realitza generalment abans de la TC és, per si mateix, un factor de risc per desenvolupar LRA-PC a causa de la deshidratació a què es sotmet al pacient. A més, el dejuni prolongat també pot amplificar la resposta a l'estrès dels pacients i fins i tot provocar ansietat, falta de cooperació, debilitat, hipoglucèmia, disminució de la pressió arterial i reaccions de xoc greus —especialment en pacients amb càncer d'edat avançada— que també contribuirien al dany renal (37). També hem de tenir en compte que en fer el dejuni programat abans d'una prova radiològica els pacients deixen de prendre els medicaments que tenen pautats, cosa que pot augmentar el risc per a la salut dels pacients amb hipertensió o diabetis o dels que necessiten qualsevol altres tipus de medicació que no s'hauria d'interrompre, afectant en molts casos de forma indirecta la funció renal.

En resum, els articles prèviament mencionats i d'altres citats al final d'aquest paràgraf demostren que no és necessari el dejú de sòlids i líquids, ni interrompre la medicació habitual del pacient, abans de la injecció de mitjans de contrast iodats per via i.v, i que específicament la ingestió de líquids abans de la TC amb contrast iodat rarament indueix a l'aparició de nàusees i vòmits i en cap cas a l'aparició d'aspiració pulmonar, que és el que històricament s'intentava evitar amb el dejú (35-39).

Barbosa et al. van estudiar la relació entre el dejuni i el contrast iodat específicament en pacients amb càncer i no van veure diferències clínicament o estadística significatives en la freqüència de reaccions adverses en pacients amb càncer amb TC amb contrast amb o sense dejuni abans de la realització de la prova (36). Les últimes guies de l'ESUR 10.0 indiquen que no és necessari el dejuni ni la interrupció de la medicació habitual abans de l'administració de mitjans de contrast iodats hipoosmolars o isoosmolars per via i.v. (23). A la nostra institució s'ha abolit la política tradicional de dejuni anterior a una TC amb contrast en tots els pacients, tret que sigui necessari per a certs tipus de proves d'imatge, bàsicament aquells pacients que requereixin que l'estómac i el budell prim estiguin buits i/o la vesícula biliar distesa.

L'ànim d'aquesta tesi és aportar evidència científica de la no inferioritat de la hidratació per via oral envers la hidratació per via intravenosa com a forma de profilaxi de la LRA-PC i conseqüentment aportar una solució universalitzable, senzilla i barata per protegir a tots els pacients amb una funció renal especialment làbil com són els pacients oncològics.

3

HIPÒTESI

3. HIPÒTESI

La hidratació per via oral no és inferior a la hidratació per via intravenosa com a mesura profilàctica de la lesió renal aguda postcontrast en pacients amb insuficiència renal crònica estadi IIIb (filtrat glomerular: 45-30ml/min/1.73m^2) als que se'ls hi realitzi una tomografia computaritzada administrant-se contrast iodat intravenós.

4

OBJECTIUS

4. OBJECTIUS

Objectiu principal

Avaluar mitjançant un estudi prospectiu i randomitzat la no inferioritat de la hidratació oral comparada amb la hidratació intravenosa en la prevenció de la lesió renal aguda postcontrast en pacients amb insuficiència renal crònica estadi IIIb (filtrat glomerular: 45-30 ml/min/1.73m^2), referits per una tomografia computaritzada amb contrast iodat (estudi NICIR).

Objectius secundaris

1. Analitzar la necessitat d'hemodiàlisi durant el mes posterior a la realització de la tomografia computaritzada amb contrast iodat, comparant l'eficàcia de la realització d'hidratació profilàctica entre les branques oral i intravenosa de l'estudi NICIR.

2. Analitzar la reversibilitat de la lesió renal aguda postcontrast 15 dies després de la realització de la tomografia computaritzada amb contrast iodat comparant l'eficàcia de la realització d'hidratació profilàctica entre les branques oral i intravenosa de l'estudi NICIR.

3. Avaluar la seguretat en ambdós grups d'hidratació de l'estudi NICIR.

4. Avaluar la no inferioritat de la hidratació oral comparada amb la hidratació intravenosa en la prevenció de la lesió renal aguda postcontrast en pacients amb IRC estadi IIIb, referits per una tomografia computaritzada amb contrast en el subgrup de pacients oncològics de l'assaig NICIR, retrospectivament.

5

MATERIAL, MÈTODES I RESULTATS

5. MATERIAL, MÈTODES I RESULTATS

5.1. Primer article que compon aquesta tesi

El primer article que compon aquesta tesi respon al objectiu principal i al primer, segon i tercer objectius secundaris:

Objectiu principal

Avaluar mitjançant un estudi prospectiu i randomitzat la no inferioritat de la hidratació oral comparada amb la hidratació intravenosa en la prevenció de la lesió renal aguda postcontrast en pacients amb insuficiència renal crònica estadi IIIb (filtrat glomerular: 45-30 ml/min/1.73m^2), referits per una tomografia amb contrast iodat (estudi NICIR).

Objectius secundaris

1. Analitzar la necessitat d'hemodiàlisi durant el mes posterior a la realització de la tomografia computaritzada amb contrast iodat, comparant l'eficàcia de la realització d'hidratació profilàctica entre les branques oral i intravenosa de l'estudi NICIR.

2. Analitzar la reversibilitat de la lesió renal aguda postcontrast quinze dies després de la realització de la tomografia computaritzada amb contrast iodat, comparant l'eficàcia de la realització d'hidratació profilàctica entre les branques oral i intravenosa de l'estudi l'NICIR.

3. Avaluar la seguretat en ambdós grups d'hidratació de l'estudi NICIR.

L'estudi NICIR publicat en aquest primer article és un estudi prospectiu, randomitzat, fase 3, de distribució aleatòria, no emmascarat, de dos grups paral·lels dissenyat per demostrar la no inferioritat de la hidratació oral versus la hidratació intravenosa com a forma de profilaxi de la LRA-PC. Els resultats estan publicats en aquest article (5):

Sebastià C, Páez-Carpio A, Guillen E, Paño B, Garcia-Cinca D, Poch E, Oleaga L, Nicolau C. Oral hydration compared to intravenous hydration in the prevention of post-contrast acute kidney injury in patients with chronic kidney disease stage IIIb: A phase III non-inferiority study (NICIR study). Eur J Radiol. 2021 Mar;136:109509. doi: 10.1016/j.ejrad.2020.109509. Epub 2021 Jan 14. PMID: 33516141.

RESUM

Objectiu

Avaluar la no inferioritat de la hidratació oral en comparació amb la hidratació intravenosa (i.v.) en la prevenció de la lesió renal aguda post-contrast (LRA-PC) en pacients amb insuficiència renal crònica (IRC) estadi IIIb als que es realitza una tomografia computaritzada (TC) amb contrast iodat injectat per via i.v.

Material i mètodes

Es tracta d'un assaig prospectiu, aleatoritzat, de fase 3, de grups paral·lels i de no inferioritat. Als pacients se'ls va assignar 1:1 per rebre profilaxi contra PC-AKI, ja fos amb hidratació oral (500 ml d'aigua dues hores abans i 2000 ml durant les 24 hores posteriors a la realització de TC amb contrast) o amb hidratació i.v. (bicarbonat sòdic (166mmol/l) 3 ml/kg/h començant una hora abans de la TC i 1 ml/kg/h durant la primera hora després de la TC amb contrast). Es van administrar 100 ml de contrast no iònic iodat en tots els casos. El resultat principal va ser la proporció de LRA-PC en les primeres 48 a 72 hores després de la TC amb contrast a ambdues branques. Els resultats secundaris van ser la presència de LRA-PC irreversible, la necessitat d'hemodiàlisi i l'aparició d'esdeveniments adversos relacionats amb la profilaxi en ambdues branques d'hidratació.

Resultats

Dels 228 pacients aleatoritzats entre gener de 2018 i gener de 2019, 114 van rebre hidratació oral i 114 van rebre hidratació i.v. i van ser avaluables. No es van trobar diferències significatives ($p< 0,05$) entre les branques de l'estudi en les característiques clíniques o els factors de risc. La taxa de LRA-PC va ser del 4,4% (IC del 95%: 1,4-9,9%) a la branca d'hidratació oral i del 5,3% (IC del 95%: 2,0-11,1%) a la branca d'hidratació i.v. La taxa de LRA-PC persistent va ser de l'1,8% (IC del 95%: 0,2-6,2%) en ambdós braços. Cap pacient va requerir diàlisi durant el primer mes després de la TC ni va experimentar efectes adversos relacionats amb el règim d'hidratació.

Conclusió

En aquells pacients amb IRC fase IIIb referits per una TC amb contrast iodat, proporcionem evidències de la no inferioritat de la hidratació oral en comparació amb la hidratació i.v. en la prevenció de la LRA-PC.

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Research article

Oral hydration compared to intravenous hydration in the prevention of post-contrast acute kidney injury in patients with chronic kidney disease stage IIIb: A phase III non-inferiority study (NICIR study)

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ABSTRACT

Objective: To evaluate the non-inferiority of oral hydration compared to intravenous (i.v.) hydration in the prevention of post-contrast acute kidney injury (PC-AKI) in patients with stage IIIb chronic kidney disease (CKD) referred for an elective contrast-enhanced computed tomography (CE-CT).

Material and Methods: This is a prospective, randomized, phase 3, parallel-group, open-label, non-inferiority trial. Patients were randomly assigned 1:1 to receive prophylaxis against PC-AKI either with oral hydration: 500 mL of water two hours before and 2000 mL during the 24 h after performing CE-CT or i.v. hydration: sodium bicarbonate (166 mmol/L) 3 mL/kg/h starting one hour before and sodium bicarbonate (166 mmol/L) 1 mL/kg/h during the first hour after CE-CT. 100 mL of non-ionic iodinated contrast was administered in all cases. The primary outcome was the proportion of PC-AKI in the first 48–72 h after CE-CT. Secondary outcomes were persistent PC-AKI, the need for hemodialysis, and the occurrence of adverse events related to prophylaxis.

Results: Of 264 patients randomized between January 2018 and January 2019, 114 received i.v. hydration and were evaluable. No significant differences were found ($p > 0.05$) between arms in clinical characteristics or risk factors. PC-AKI rate was 4.4 % (95 %CI: 1.4−9.9 %) in the oral hydration arm and 5.3 % (95 %CI: 2.0−11.1%) in the i.v. hydration arm. The persistent PC-AKI rate was 1.8 % (95 %CI: 0.2−6.2 %) in both arms. No patient required dialysis during the first month after CE-CT or had adverse effects related to the hydration regime.

Conclusion: In those with stage IIIb CKD referred for an elective CE-CT, we provide evidence of non-inferiority of oral hydration compared to i.v. hydration in the prevention of PC-AKI.

1. Introduction

Post-contrast acute kidney injury (PC-AKI) is defined as an increase in serum creatinine (sCr) ≥ 0.3 mg/dL (26.5 μmol/l) or ≥ 1.5 times baseline occurring within 48−72 h of intravascular administration of iodinated contrast media, most commonly by the performance of a contrast-enhanced CT scan (CE-CT) [1,2]. Although PC-AKI is a condition always present in the minds of both referring physicians and radiologists, recent retrospective studies have suggested that the risk of PC-AKI after intravenous (i.v.) iodinated contrast media may have been overestimated [3–5]. Pre-existing chronic kidney disease (CKD) is the most critical patient-related PC-AKI risk factor [6]. Traditional non-renal risk factors such as diabetes, hypertension, cardiovascular disease, and nephrotoxic medications are now considered non-specific risk factors for PC-AKI [6].

Intravenous hydration is currently the cornerstone of PC-AKI prophylaxis. Recommended methods of i.v. hydration varies according to the consulted guideline. No single pharmaceutical intervention has been shown to prevent the occurrence of PC-AKI effectively [7]. The AMACING trial and the Kompas trial, both recent non-inferiority studies, questioned the effectiveness of i.v. hydration in the prophylaxis of PC-AKI in patients with stage IIIb CKD [8,9]. This fact has led to several radiological societies, including the American College of Radiology and the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) to reduce the PC-AKI risk threshold from 45 to 30 mL/min/1.73m2 of estimated glomerular filtration rate (eGFR) as an indication for preventive treatment before iodinated i.v. contrast injection [1,10]. However, these recent less conservative recommendations are not accepted by all the radiological associations, some of them promoting the maintenance of the threshold of 45 mL/min/1.73m2 of eGFR as a risk factor for PC-AKI [11,12]. The lack of definitive scientific evidence has motivated a cautious attitude in the nephrological community, concluding that it is too early to declare the non-obligation or ineffectiveness of hydration in the prevention of PC-AKI [11,12].

A possible solution for these patients may be a safer and easier-to-administer prophylactic alternative to i.v. hydration. Although the literature is sparse, a recent meta-analysis indicated oral hydration is as efficacious as i.v. hydration for renal prophylaxis of PC-AKI [13].

The present study aims to prospectively evaluate the non-inferiority of oral hydration compared to i.v. hydration in the prevention of PC-AKI in outpatients with stage IIIb CKD referred for an elective CE-CT.

2. Material and methods

2.1. Trial design

The NICIR study is a prospective, randomized, phase 3, parallel-group, open-label, non-inferiority study designed to assess the non-inferiority of oral hydration versus i.v. hydration as a prophylactic measure of PC-AKI in outpatients of both genders and over 18 years of age with stage IIIb CKD and referred for an elective CE-CT. Stage IIIb CKD was defined as an eGFR between 30 and 44 mL/min/1.73m2, estimated by the Modification of Diet in Renal Disease formula [14].

Exclusion criteria were pregnancy, lactation, associated acute kidney disease, contraindication for hydration or iodinated contrast agent, and administration of more than one dose of i.v. iodinated contrast within **one week** before the measurement of sCr.

The Institutional Review Board and the Ethical Committee of our institution approved this trial protocol. All patients included voluntarily signed informed consent. An independent data and safety monitoring board periodically reviewed the preliminary results of the trial. The NICIR study was registered in ClinicalTrials.gov (NCT02872155) and EudraGMP (CT 2016-002033.33).

In our hospital, eGFR levels of all patients referred for a CE-CT appeared on the referring physician's electronic order. Patients with a stage IIIb CKD documented in the three months prior to a scheduled CT were automatically referred to our radiological nursing consultation for evaluation. The clinical trial was explained to each patient and, once the informed consent was signed, values of sCr and eGFR were recorded, and each patient was subsequently randomized to one of two arms:

1 Oral hydration: 500 mL of water two hours before CE-CT and 2000 mL in the following 24 h after performing CE-CT.
2 Intravenous hydration: sodium bicarbonate (166 mmol/L) 3 mL/kg/h starting one hour before CE-CT and sodium bicarbonate (166 mmol/L) 1 mL/kg/h during the hour after CE-CT.

Our study's short-term i.v. hydration protocol is based on a scheme that proved to be as effective as long-term i.v. hydration schemes in a randomized study published by Kooiman et al. [15]. For oral hydration, we follow Kong et al. published treatment, as it has been shown to be effective in preventing PC-AKI in patients who underwent coronary angiography [16].

All patients assigned to the oral hydration arm were instructed to drink water following the predetermined treatment. In the i.v. hydration arm patients were asked to come to the hospital for i.v. hydration 1 h before the CE-CT. All patients received 100 mL of non-ionic, iodinated contrast agent Iohexol (Omnipaque 300 mg I/mL intravenous solution, GE Healthcare Bio-Sciences, S.A.U).

Age, gender, renal function, clinical indication for CT (differentiating oncological versus non-oncological indication), and risk factors for renal damage, such as diabetes, hypertension, cardiovascular disease, nephrotoxic medications, and baseline sCR and eGFR (at least three months prior CE-CT) were obtained from the electronic medical records of each patient. All patients underwent a blood test to determine sCr and eGFR between 48 and 72 h after performing the CE-CT. Patients assigned to the oral hydration arm were contacted to confirm the hydration regime's proper administration after CE-CT.

Differences between baseline and post-examination sCr values were assessed to evaluate the presence of PC-AKI, which was defined as an increase in serum creatinine ≥ 0.3 mg/dl (26.5 μmol/l) or ≥1.5 times baseline level occurring within 48−72 h of intravascular administration of iodinated contrast media. In patients who developed PC-AKI, a second sCr test was performed 15 days after CE-CT to determine the reversibility or persistency of PC-AKI. All patients with PC-AKI were referred to a consultant nephrologist to detect any concomitant cause of AKI and close monitoring renal function. The need for hemodialysis less than one month after CE-CT and the presence of grade 3 adverse events related to hydration were also assessed.

PC-AKI rates in patients assigned in both the oral hydration and i.v. hydration arms were considered the primary outcome. Reversibility of PC-AKI within the first 15 days after CE-CT, the need for hemodialysis within the first month after completion of the CE-CT, and the occurrence of grade 3 adverse events related to hydration were assessed as secondary outcomes.

2.2. Statistical methods

We used 1:1 simple randomization using C-Disk platform with no stratification factors. The technician and radiologist were blinded to allocation, but patients were not blinded to allocation given the differences in administration. This study was designed as a non-inferiority trial with an estimated i.v. hydration PC-AKI rate of 9 % and a 9 % non-inferiority margin (indicating ≥18 % to be inferior), no expected difference between arms, with a one-sided Type I error rate of 5% and 125 patients per arm [17]. An 80 % power was established to declare oral hydration non-inferior to i.v. hydration.

We checked for balance between arms with Fisher's Exact Test and the Wilcoxon Rank Sum test, where appropriate. Rates of PC-AKI were estimated overall and by reversibility, along with 95 % exact confidence intervals. We used 95 % confidence intervals to align with standard presentation of estimates. We also estimated the upper bound of the 90 % confidence interval to align with the planned one-sided Type I error rate.

After assessing balance between arms, we performed post-hoc logistic regression analyses to assess the association between these factors and the outcome. Although we had a limited number of events, we performed bivariable (arm + each unbalanced factor) and multivariable analyses (arm + all unbalanced factors), controlling for the unbalanced factors.

Two-sided p-values less than 0.05 were considered statistically significant. All analyses were performed with SAS 9.4 TS1M6 (The SAS Institute).

3. Results

Between January 2018 and January 2019, a total of 264 patients were evaluated for analysis after meeting inclusion criteria and signing informed consent. Eighteen patients were excluded in the i.v. hydration arm and 18 in the oral hydration arm. The most frequent reason for

Abbreviations: PC-AKI, Post-contrast acute kidney injury; sCR, Serum creatinine; CT, Computed tomography; CE-CT, Contrast-enhanced CT; i.v., intravenous; CKD, Chronic kidney disease; ESUR, European Society of Urogenital Radiology; eGFR, estimated glomerular filtration rate.

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exclusion was spontaneous worsening of kidney function before CE-CT (8 in oral hydration arm and 9 in i.v. hydration arm). It should be noted that some patients signed the informed consent three months before the scheduled CT, which means that during this period, kidney function could worsen due to several causes. Other reasons for exclusion are pointed in Fig. 1.

3.1. Patient characteristics

The final study sample included 228 patients, of whom 114 received oral Hydration and 114 received i.v. hydration. Overall, median age was 75 years (Range: 35–96) and 75 patients (33 %) were female. No significant differences were found between oral hydration versus i.v. hydration arms for age (median 74 vs. 76 years, p = 0.24), gender (male 65 % vs. 59 %, p = 0.57), diabetes (38 % vs. 46 %, p = 0.28), hypertension (68 % vs. 78 %, p = 0.13), cardiovascular disease (33 % vs. 42 %, p = 0.22), history of cancer (72 % vs. 81 %, p = 0.16), or nephrotoxic medications (13 % vs. 13 %, p > 0.95). However, baseline laboratory values differed between cohorts. Patients who received oral hydration had higher eGFR (Median 39.0, (IQR: 35.0–42.0) compared to patients in the i.v. hydration arm (Median 36.0, (IQR: 32.0–40.0), p = 0.002) and baseline creatinine was lower in the oral hydration arm (Median 1.6, (IQR: 1.5–1.8) compared to i.v. hydration patients (Median 1.7, IQR (IQR: 1.5–1.9), p = 0.006 (Table 1).

Although differences were noted in eGFR (Median 39.0 vs. 36.0, p = 0.002) and creatinine (Median 1.6 vs. 1.7, p = 0.005) 48 h post-CT in the oral versus i.v. hydration groups, this was likely a function of higher baseline laboratory values. No significant differences were found in the variations from baseline to post-CT assessments for eGFR (0.0 vs. 0.0, p = 0.17) or creatinine (−0.0 vs. 0.0, p = 0.14) (Table 1).

3.2. PC-AKI

Fourteen patients in total presented with AKI during the study. Three patients had other causes for AKI (1 pyelonephritis and 2 upper urinary tract obstruction). Eleven patients in total (5 %) experienced PC-AKI. Patients who received oral hydration had a PC-AKI rate of 4.4 % (95CI:1.4–9.9 %), with 5 patients who experienced PC-AKI. In the i.v. hydration arm, the PC-AKI rate was 5.3 % (95CI:2.0–11.1 %), with 6 patients who experienced PC-AKI (Table 2). For i.v. hydration, the upper bound of the 90 % confidence interval was 10.12 %, which the estimate of PC-AKI for oral hydration fell within.

PC-AKI was reversible in 3 patients (3 %) and irreversible in 2 patients (2 %) in the oral hydration arm. In the i.v. hydration arm, reversible PC-AKI was reported in 4 patients (4 %) and irreversible PC-AKI in 2 patients (2 %) (Table 2).

3.3. Controlling for confounding

In post-hoc analyses, no significant association was found between baseline eGFR (OR: 0.98, 95 %CI: 0.86–1.12, p = 0.79) or baseline creatinine (OR: 0.64, 95 %CI: 0.06–6.97, p = 0.71). In bivariable and multivariable models, the relationship between arm and PC-AKI remained consistent after controlling these unbalanced factors (OR: 0.78–0.85) (Table 3).

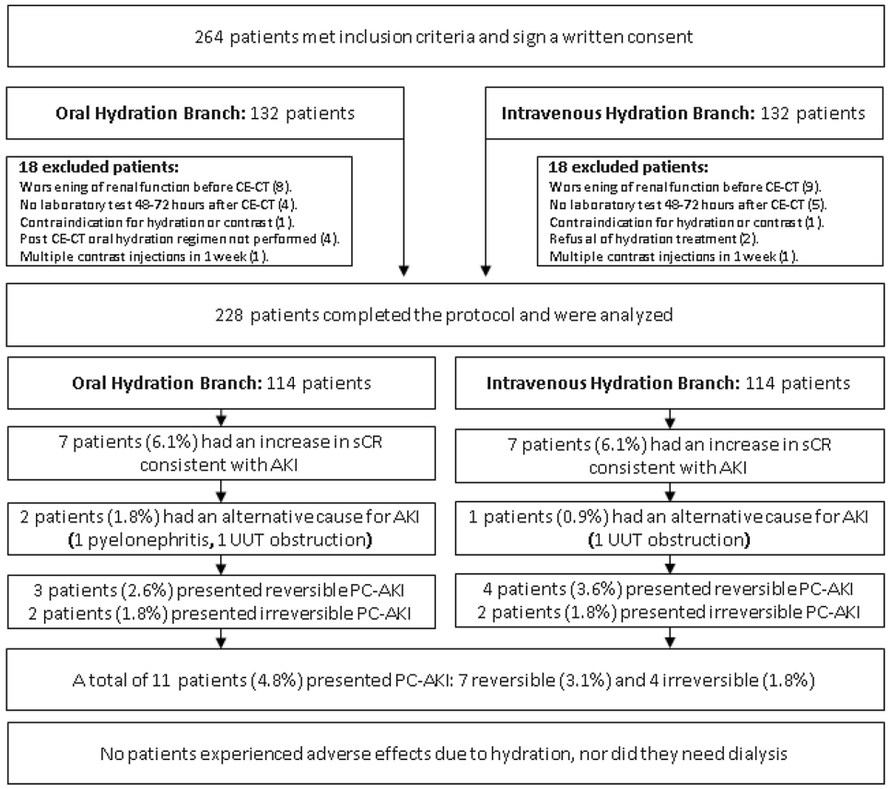

Fig. 1. Study Design. CE-CT: Contrast-Enhanced Computed Tomography. sCR: Serum Creatinine. PC-AKI: Post-Contrast Acute Kidney Injury.

Table 1
Patient and Clinical Characteristic.

		All Patients	Oral Hydration	i.v. Hydration	p-value
Patients		228	114 (50)	114 (50)	
Age, *years*	Median (Range)	75 (35–96)	74 (35–96)	76 (48–93)	024
Gender	Male	153 (67.1)	74 (64.9)	76 (59.3)	0.57
	Female	75 (32.9)	40 (35.1)	35 (30.7)	
Associated Risk Factors					
Diabetes Mellitus		95 (41.7)	43 (377)	52 (456)	0.28
Arterial Hypertension		167 (73.2)	78 (684)	89 (781)	0.13
Cardiovascular Disease		86 (37.7)	38 (333)	48 (421)	0.22
Oncological History		174 (76.3)	82 (71.9)	92 (80.7)	0.16
Nephrotoxic medications		30 (13.2)	15 (132)	15 (132)	>0.95
Laboratory Values					
Baseline eGFR	Median (Range)	37.0 (25.0–44.0)	39.0 (28.0–44.0)	36.0 (25.0–44.0)	**0.002**
eGFR 48 h Post-CT	Median (Range)	37.0 (19.4–73.0)	39.0 (19.4–73.0)	36.0 (23.0–63.0)	**0002**
eGFR Difference from Baseline	Median (Range)	0.0 (-27.2–30.0)	0.0 (-27.2–30.0)	0.0 (-18.0–28.0)	017
Baseline sCR	Median (Range)	1.7 (1.1–2.2)	1.6 (1.1–2.2)	1.7 (1.2–2.2)	**0006**
sCR 48 h Post-CT	Median (Range)	1.7 (0.8–3.3)	1.6 (0.8–3.3)	1.7 (1.1–2.5)	**0005**
sCR Difference from Baseline	Median (Range)	0.0 (-0.8–1.1)	0.0 (-0.5–1.1)	0.0 (-0.8–0.5)	014

i.v.: Intravenous. CT: Computed Tomography. eGFR: Estimated Glomerular Filtration Rate. sCR: Serum Creatinine.
Numbers represent frequency with percent of column total unless otherwise stated.

Table 2
Rates of PC-AKI.

		Oral Hydration		i.v. Hydration	
		% (95 %CI)	N	% (95 %CI)	N
PC-AKI	Yes	4.4 % (1.4–9.9 %)	5/114	5.3 % (2.0–11.1 %)	6/114
PC-AKI Reversibility Status	Irreversible	1.8 % (0.2–6.2 %)	2/114	1.8 % (0.2–6.2 %)	2/114
	Reversible	2.6 % (0.5–7.5 %)	3/114	3.5% (1.0–8.7 %)	4/114

PC-AKI: Post-Contrast Acute Kidney Injury. Tomography. **i.v.:** Intravenous.

4. Discussion

The results of our study showed a lower PC-AKI rate in the oral hydration arm (4.4 %) compared to the in the i.v. hydration arm (5.3 %). PC-AKI rate in the entire sample was 4.8 %. These rates are comparable to those reported in studies with prophylactic i.v. hydration schemes similar to ours and superior compared to studies with more extended i.v. hydration prophylaxis regimens [7,15]. Also, no patient required dialysis following CE-CT or had adverse events due to either hydration regimen.

The pathogenesis of PC-AKI is related to the direct damage caused by iodinated contrast to the epithelial and endothelial cells, followed by inflammation, oxidative stress, osmotic load, and finally, hypoperfusion and hypoxia. Theoretically, both i.v. hydration and oral hydration should protect against PC-AKI by improving renal blood flow and increasing e**GFR**, which could minimize epithelial cell exposure to contrast, decrease urine viscosity, prevent tubular obstruction, and expedite the elimination of contrast media. Moreover, oral hydration could additionally accelerate renal water excretion by osmoregulatory mechanisms [18]. The physiological action of oral hydration, by suppressing the release of vasopressin, leads to a rapid increase in diuresis and therefore provides short-term renal protection [13,18,19].

Our study's oral hydration and i.v hydration schemes correspond to those reflected in our hospital guidelines. These are prepared jointly by the radiology and nephrology services, following the most recent published protocols [16,20]. The protocol designed for i.v. hydration is similar to a short-term treatment that proved as equally effective as long-term treatments in a randomized study [15]. This short treatment is now indicated in the last ESUR guidelines [6]. For oral hydration, we follow Kong et al. published treatment, as it has been shown to be effective in preventing PC-AKI in patients who underwent coronary angiography [16]. As Kong et al. stated, oral hydration must begin at least one hour before the CE-CT and should be followed with a prolonged hydration plan after the CE-CT to ensure its effectiveness [18].

Published meta-analyses have suggested that oral hydration might be as effective as i.v. hydration in the prevention of PC-AKI [13,17,19,21]. These analyzed the results of studies with significant heterogeneity, addressing multiple types of procedures (cardiac catheterization, CE-CT, angiography for peripheral vascular disease, etc.). The first meta-analysis conducted on this topic included studies where ionic iodinated contrast was used. Ionic iodinated contrast is not currently used due to its high nephrotoxicity, which could affect their overall conclusions [22,23]. Also, most patients included in these meta-analyses

Table 3
Associations with PC-AKI, Controlling for Unbalanced Baseline Factors.

	Univariable			Bivariable: sCR			Bivariable: eGFR			Multivariable		
	OR	(95 % CI)	p-value	OR	(95 % CI)	p-value	OR	(95 % CI)	p-value	OR	(95 % CI)	p-value
Arm												
Oral i.v.	0.83	(0.24–2.79)	0.76	0.78	(0.23–2.71)	0.70	0.85	(0.25–2.94)	0.80	0.82	(0.24–2.84)	0.75
	REF			—			—			—		
Baseline sCR	0.64	(0.06–6.97)	0.71	0.58	(0.05–6.65)	0.66	—			0.34	(0.02–7.05)	0.49
Baseline eGFR	0.98	(0.86–1.12)	0.79	—			0.99	(0.86–1.12)	0.83	0.95	(0.81–1.12)	0.56

PC-AKI: Post-Contrast Acute Kidney Injury. **i.v.:** Intravenous. **sCR:** Serum Creatinine. **eGFR:** Estimated Glomerular Filtration Rate.

had normal or mild renal dysfunction, and oral hydration administration protocols varied from study to study, differing in hydration rate, time, and total volume, as well as the small number of patients included in most series [16,24–27].

To the best of our knowledge, this is the first prospective study comparing the non-inferiority of oral hydration versus i.v. hydration after referral for a CE-CT (only one procedure and only i.v. contrast injection) in patients with stage IIIb CKD (only moderate to severe CKD). Only two studies on oral hydration effectiveness have included patients referred to a CE-CT, both with some drawbacks: Dussol et al. included procedures other than CE-CT, and Garcia-Ruiz et al. did not compare oral hydration with i.v. hydration [28,29].

Oral hydration seems to be a reasonable prophylaxis strategy for moderate to severe CKD patients referred for a CE-CT. Oral hydration improves patient compliance and comfort, as it is more easily administered. When considering cost, oral hydration seems to be a preferable option. Prophylactic treatment with oral hydration, as is described in this study, is now included in the protocol for performing all CE-CT in our hospital, since preparative fasting before CE-CT is no longer required. In 2012, Lee et al. questioned the need for preparative fasting before CE-CT, noting a decrease in the discomfort and inconvenience of patients who were not subjected to programmed fasting [30]. These authors found no cases of aspiration pneumonia attributable to the ingestion of clear inert fluid before non-ionic iodinated CE-CT. It is possible that this complication is specific to the injection of ionic iodinated contrast, now excluded from clinical practice. Furthermore, Barbosa et al. showed that fasting before CE-CT increased nausea and vomiting, adding that fasting should be omitted since reducing hydration may increase the risk of subsequent PC-AKI [31].

This study has several limitations. First, PC-AKI rates were lower than predicted when designing the trial. We found no apparent cause for this result, which may be due to either sample selection, closer monitoring, or even chance. Additionally, the margin of inferiority in the oral hydration arm was equal to that of the control, indicating that even twice the current rate in the i.v. hydration arm would be considered non-inferior. Nevertheless, this study was conducted on well over 200 patients, demonstrating PC-AKI rates of 4.4 % (95 %CI: 1.4−9.9%) in the oral hydration arm and 5.3 % (95 %CI: 2.0−11.1%) in the i.v. hydration arm. Moreover, given the one-sided 5 % type I error rate, the i.v. arm's 90 % upper bound was 10.2 %, which was higher than the 4.4 % observed rate, thus demonstrating the non-inferiority of oral hydration compared with i.v. hydration under the parameters established in our study.

We also did not anticipate differences in laboratory values at baseline, which led to unbalanced groups due to non-stratified randomization. That said, it is possible that the non-inferiority demonstrated in this study may be a function of confounding, although it seems unlikely that the perfect balance of these groups produced a 9 % higher rate. Nonetheless, future studies should consider using stratified block random sampling.

Furthermore, although the PC-AKI rate fell within the expected range, it was on the lower end, precluding us from having a sufficient sample size to fully explore confounding and potential interaction effects/subgroups. Future studies should also take into account the rarity of PC-AKI in addition to the differences between groups. Finally, we have to consider the fact that the intrinsic natural variations in creatinine serum levels make it challenging to define which variations are directly caused by iodinated contrast medium administration.

5. Conclusion

In patients with CKD stage IIIb referred for CE-CT, our study demonstrated that the rate of PC-AKI in the oral hydration arm was not more significant than that in the i.v. hydration arm, indicating the non-inferiority of this administration route. Oral hydration could be a convenient and easy-to-use prophylactic method in the prevention of PC-AKI in patients with stage IIIb CKD undergoing a CE-CT, adding an option to the current debate in radiological and nephrological organizations about the correct prevention of PC-AKI.

CRediT authorship contribution statement

Carmen Sebastià: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Alfredo Páez-Carpi:** Formal analysis, Writing - original draft, Writing - review & editing. **Elena Guillen:** Formal analysis, Resources, Data curation, Investigation, Writing - original draft. **David Garcia-Cinca:** Methodology, Formal analysis, Data curation. **Esteban Poch:** Conceptualization, Investigation, Visualization, Supervision. **Laura Oleaga:** Conceptualization, Investigation, Visualization, Writing - original draft, Supervision. **Carlos Nicolau:** Conceptualization, Investigation, Visualization, Writing - original draft, Supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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5.2. Segon article que compon aquesta tesi

El segon article que compon aquesta tesi respon al quart objectiu secundari

4) Avaluar la no inferioritat de la hidratació oral comparada amb la hidratació intravenosa en la prevenció de la lesió renal aguda postcontrast en pacients amb insuficiència renal crònica estadi IIIb referits per una tomografia computaritzada amb contrast ambulatòria en el subgrup de pacients oncològics de l'estudi NICIR, retrospectivament.

Els resultats estan publicats en aquest article (6).

Sebastià C, Páez-Carpio A, Guillen E, Paño B, Arnaiz JA, de Francisco AJL, Nicolau C, Oleaga L. Oral hydration as a safe prophylactic measure to prevent post-contrast acute kidney injury in oncologic patients with chronic kidney disease (IIIb) referred for contrast-enhanced computed tomography: subanalysis of the oncological group of the NICIR study. Support Care Cancer (2021). https://doi.org/10.1007/s00520-021-06561-7

RESUM

Objectiu

L'objectiu d'aquest estudi és avaluar l'eficàcia de la hidratació oral en comparació amb la hidratació intravenosa (i.v.) en la prevenció de la lesió renal aguda postcontrast (LRA-PC) en pacients amb insuficiència renal crònica (IRC) estadi IIIb, que són sotmesos a una tomografia computaritzada (TC) amb contrast iodat en el subgrup oncològic de l'estudi NICIR.

Material i mètodes

Es realitza una subanàlisi retrospectiva del subgrup oncològic (174/228 pacients, 74%) de la base de dades de pacients inclosos en l'estudi NICIR per valorar la no inferioritat de la hidratació oral versus la hidratació intravenosa com a mesura profilàctica de la LRA-PC. Els pacients van rebre profilaxi de la LRA-PC amb hidratació oral (500 ml d'aigua dues hores abans i 2000 ml durant les 24 hores posteriors al CE-CT) o hidratació intravenosa (bicarbonat sòdic (166 mmol /l) 3 ml/kg/h començant una hora abans de la TC i 1 ml/kg/h durant la primera hora després de la TC). L'objectiu principal va ser comparar la proporció de casos de LRA-PC en les primeres 48 a 72 hores després de la TC amb contrast en els dos grups d'hidratació. Els objectius secundaris van ser comparar les tasses de LRA-PC persistent, la necessitat d'hemodiàlisi i l'aparició d'esdeveniments adversos relacionats amb la profilaxi en cada grup.

Resultats

Dels 174 pacients inclosos en aquesta subanàlisi, 82 van rebre hidratació oral i 92 van rebre hidratació i.v. No hi va haver diferències significatives en les característiques clíniques ni en els factors de risc entre els dos braços de l'estudi. En general, la taxa de LRA-PC va ser del 4,6% (8/174 pacients), essent el 3,7% en el braç d'hidratació oral (3/82 pacients) i el 5,4% (5/92 pacients) en el braç d'hidratació i.v. La taxa de LRA-PC persistent va ser de l'1,8% (1/82 pacients) al braç d'hidratació oral i del 3,3% (3/92 pacients) al braç d'hidratació i.v. Cap pacient va requerir diàlisi durant el primer mes després de la TC o va tenir efectes adversos relacionats amb el règim d'hidratació.

Conclusió

En pacients oncològics amb IRC estadi IIIb derivats per a la realització d'una TC amb contrast, la taxa de LRA-PC en aquells pacients que rebien hidratació oral no va diferir significativament de la dels pacients que van rebre hidratació i.v.

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ORIGINAL ARTICLE

Oral hydration as a safe prophylactic measure to prevent post-contrast acute kidney injury in oncologic patients with chronic kidney disease (IIIb) referred for contrast-enhanced computed tomography: subanalysis of the oncological group of the NICIR study

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Abstract

Background The objective of this study is to evaluate oral hydration compared to intravenous (i.v.) hydration in the prevention of post-contrast acute kidney injury (PC-AKI) in the oncologic subgroup of patients with stage IIIb chronic kidney disease (CKD) included in the NICIR study referred for elective contrast-enhanced computed tomography (CE-CT).

Material and methods We performed a retrospective subanalysis of the oncological subgroup (174/228 patients, 74%) from a continuous prospective database of patients included in the recently published non-inferiority NICIR study. Patients received prophylaxis against PC-AKI with either oral hydration (500 mL of water 2 h before and 2000 mL during the 24 h after CE-CT) or i.v. hydration (sodium bicarbonate (166 mmol/L) 3 mL/kg/h starting 1 h before and 1 mL/kg/h during the first hour after CE-CT). The primary outcome was to compare the proportion of PC-AKI in the first 48 to 72 h after CE-CT in the two hydration groups. Secondary outcomes were to compare persistent PC-AKI, the need for haemodialysis, and the occurrence of adverse events related to prophylaxis in each group.

Results Of 174 patients included in the subanalysis, 82 received oral hydration and 92 received i.v. hydration. There were no significant differences in clinical characteristics or risk factors between the two study arms. Overall the PC-AKI rate was 4.6% (8/174 patients), being 3.7% in the oral hydration arm (3/82 patients) and 5.4% (5/92 patients) in the i.v. hydration arm. The persistent PC-AKI rate was 1.2% (1/82 patients) in the oral hydration arm and 3.3% (3/92 patients) in the i.v. hydration arm. No patient required dialysis during the first month after CE-CT or had adverse effects related to the hydration regime.

Conclusion In oncological patients with stage IIIb CKD referred for elective CE-CT, the rate of PC-AKI in those receiving oral hydration did not significantly differ from that of patients receiving i.v. hydration.

Keywords Acute renal event · Water · Iodinated contrast media · Iodine/adverse effects · Cancer · Contrast-induced acute kidney injury · Contrast-induced nephopathy · Computed tomography

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Background

Intravenous (i.v.) non-ionic iodinated contrast media are commonly used in computed tomography (CT) to evaluate oncologic patients. Contrast-enhanced computed tomography (CE-CT) plays an important role in the natural history of patients with cancer. CE-CT is essential to correctly characterise and stage the disease and to monitor response to oncological treatments and the risk of progression or relapse during follow-up.

Nephrotoxicity by iodinated contrast media, known as post-contrast acute kidney injury (PC-AKI), is defined as an

increase in serum creatinine (sCr) ≥ 0.3 mg/dL (26.5 µmol/L) or ≥ 1.5 times the baseline level occurring within 48–72 h of iodinated contrast media administration, in the absence of concurrent causes [1]. Pre-existing chronic kidney disease (CKD), dehydration, and acute kidney disease (AKI) are the most critical patient-related PC-AKI risk factors [2].

It is widely accepted that oncological patients have a higher risk of developing AKI, which may be as high as 17.5% at 1 year and up to 27% at 5 years after cancer diagnosis [3]. Age, type of tumour, type of oncologic treatment, use of nephrotoxic agents, dehydration, pre-existing kidney disease, and iodinated contrast media nephrotoxicity, among other factors, may influence the presence or absence of AKI in these patients [4].

With the increase in life expectancy, there has been a rise in the number of cancer patients, many of whom have multiple risk factors leading to impaired renal function (diabetes, hypertension, cardiovascular diseases, nephrotoxic medications, among others). Moreover, the mechanism for the development of AKI may also depend on the type of tumour. Some, such as haematological malignancies, may cause AKI due to an overproduction and filtration of toxic light chains (leading to tubular injury), infiltration of the renal parenchyma, or due to their association with secondary glomerulonephritis. Other tumours, especially those of nearby organs, can directly invade the urinary tract, causing obstructive nephropathy. Furthermore, some patients may develop AKI after undergoing partial or total nephrectomy or urinary diversion. Finally, multiple pathophysiological mechanisms related to cancer itself, such as volume depletion, sepsis, or several paraneoplastic syndromes, may cause AKI [4].

Nephrotoxicity by cancer therapies is another aspect that must be taken into account because of its increasing importance in clinical practice. Conventional chemotherapy with cytotoxic agents may cause kidney toxicity mainly by tubular excretion or vascular damage. New recently developed oncology drugs block specific molecules involved in tumour growth and progression (targeted therapy), thus minimising the side effects of conventional chemotherapy. Nevertheless, such signalling pathways are also active in a healthy organism, and their inhibition may be accompanied by side effects. In this regard, wide ranges of toxicities affecting various parts of the nephron have been reported with these novel targeted therapies, one of the most common disorders being acute interstitial nephritis. In this regard, both conventional and targeted therapies can affect any segment of the nephron [5].

In addition to the above, cancer patients need consecutive imaging tests to monitor disease progression, thus receiving repeated exposure to iodinated contrast [6]. However, iodinated contrast media have historically been avoided in patients with reduced kidney function due to the perceived risk of PC-AKI. This circumstance may be detrimental to these patients, given the delay in diagnosis, staging, and follow-up. Furthermore, recent articles based on propensity score matching studies have stated that PC-AKI has not only been overestimated but may even be nonexistent [7–10].

Hydration, either with i.v. saline or bicarbonate, is currently the cornerstone of PC-AKI prophylaxis [11]. However, oral hydration may also be an option in the prophylaxis of PC-AKI, as we stated in the results of our NICIR trial, published recently, and in a recently published meta-analysis [12, 13].

The NICIR study is the first prospective randomised phase III non-inferiority study to demonstrate that oral hydration is non-inferior to i.v. hydration in the prevention of PC-AKI in patients with stage IIIb CKD referred for elective CE-CT [12]. One hundred seventy-four of the patients enrolled in the aforementioned NICIR study were oncologic patients. The present retrospective analysis aims to determine whether oral hydration is effective in the prevention of PC-AKI in the subgroup of oncologic patients.

Material and methods

We retrospectively analysed the subgroup of oncological patients of the NICIR study obtained from a continuous prospective patient database. The NICIR study included patients of both genders over 18 years of age with stage IIIb CKD referred for elective CE-CT. Stage IIIb CKD was defined as an estimated glomerular filtration rate (eGFR) between 30 and 44 mL/min/1.73m^2, determined by the Modification of Diet in Renal Disease formula [14]. The exclusion criteria were as follows: refusal to participate in the study, pregnancy and lactation, associated AKI, contraindication for hydration or iodinated contrast agent administration, and more than one i.v. iodinated contrast test performed within 48–72 h.

This retrospective study was approved by the Institutional Review Board and the Ethical Committee of our institution. Signed consent was not needed for this retrospective analysis. Nonetheless, all the patients included had voluntarily provided consent for participation in the previous prospective trial.

The following data were retrospectively obtained from the electronic medical records of all the patients: age, gender, risk factors associated with AKI (diabetes, hypertension, cardiovascular disease), tumour type, oncologic disease status, active oncological treatment, and nephrotoxic medications, differentiating between non-oncological and oncological treatments. Finally, we recorded sCR and eGFR at baseline (at least 3 months before CE-CT) and between 48 and 72 h after CE-CT.

Patients received one of these prophylactic therapies based on schedules published in the literature [15, 16]:

1. Oral hydration: 500 mL of water 2 h before CE-CT and 2000 mL in the following 24 h after the scan.
2. i.v. hydration: sodium bicarbonate (166 mmol/L) 3 mL/kg/h starting 1 h before CE-CT and sodium bicarbonate (166 mmol/L) 1 mL/kg/h during the hour after CE-CT.

For the CE-CT, all patients received 100 mL of the non-ionic hypotonic iodinated contrast agent Iohexol (Omnipaque 300 mg I/mL i.v. solution, GE Healthcare Bio-Sciences, S.A.U).

Differences between baseline and post-examination sCR values were assessed to evaluate the presence of PC-AKI, which was defined as an increase in sCR ≥ 0.3 mg/dL (26.5 µmol/L) or ≥ 1.5 times the baseline level occurring within 48–72 h of iodinated contrast media administration [1]. In patients who developed PC-AKI, a second sCR test was performed 15 days after CE-CT to determine the persistence or reversibility of PC-AKI. All patients with PC-AKI were referred to a consultant nephrologist to detect any concomitant cause of AKI and for close monitoring of renal function. The need for haemodialysis less than 1 month after CE-CT and the presence of grade 3 adverse events related to hydration were also assessed.

Statistical methods

We checked for balance between the two arms with the Fisher's exact test and the Wilcoxon rank sum test in the oncological cohort of the NICIR study, where appropiated [12]. Rates of PC-AKI were estimated overall and by reversibility, along with 95% exact confidence intervals (95%CI). We used 95%CI to align with the standard presentation of stimates. We also estimated the upper bound of the 90% confidence interval (90%CI) to align with the planned one-sided type I error rate.

After assessing balance between arms, we performed a post hoc logistic regression analysis to assess the association between these factors and outcome. Although we had a limited number of events, we performed bivariable (arm + each unbalanced factor) and multivariable analyses (arm + all unbalanced factors), controlling for the unbalanced factors. We also assessed the interaction between arm and cancer history with PC_AKI, and provided stimates stratified by cance history.

Two-sided *p*-values less than 0.05 were considered statistically significant. All analyses were performed with SAS 9.4 TS1M6 (The SAS Institute, Cary, NC).

Results

The final sample of cancer patients included 174 patients, 82 of whom 82 received oral hydration and 92 received i.v. hydration. Overall, the median age was 75 years (range 35–90), and 55 patients (32%) were female. Arms were partially balanced in baseline factors. Patients who received oral hydration were younger (median 73 (interquartile range [IQR] 67–80)) than those who received i.v. hydration (median 76 (IQR: 70–82)), $p = 0.03$. No other significant differences were found for the remaining clinical characteristics or associated risk factors ($p = 0.09$–0.87). However, baseline laboratory values differed between cohorts. Patients who received oral hydration had a higher eGFR (median 39.0, IQR: 35.0–42.0) compared to patients receiving i.v. hydration (median 36.0 (IQR: 32.0–40.0)), $p < 0.001$. Additionally, baseline sCR values were slightly lower in the oral hydration arm (median 1.6 (IQR: 1.4–1.8)) compared to i.v. hydration patients (median 1.7, IQR: 1.5–1.9), $p = 0.07$. Differences were also detenoted in eGFR (median 39.5 vs. 36.0, $p < 0.001$) and sCR values (median 1.6 vs. 1.7, $p = 0.013$) 48–72 h after CE-CT in the oral versus hydration groups (Tables 1 and 2, Fig. 1).

PC-AKI

Eight patients (4.6%) experienced PC-AKI. Three patients in the oral hydration arm developed PC-AKI, resulting in a PC-AKI rate of 3.7% (95%CI: 0.8–10.3%). In the i.v. hydration arm, the PC-AKI rate was 5.4% (95CI:1.8–12.2%), with 5 patients developing PC-AKI (Table 2). For i.v. hydration, the upper bound limit of the 90%CI was 11.1%, which covered the estimate of PC-AKI for the oral hydration arm (3.7% < 11.1%) (Table 3).

PC-AKI was reversible for 2 patients (2.4%) and was irreversible in 1 patient (1.2%) in the oral hydration arm, while in the i.v. hydration arm, PC-AKI was irreversible in 3 patients (3.3%) and reversible in 2 patients (2.2%) (Table 3).

Not patients experienced adverse effects due to hydration, nor did they need dialysis.

Control for confounding

In the post hoc analyses, no significant association was found between age (odds ratio [OR]: 0.99, 95%CI: 0.94–1.06, $p = 0.85$), baseline eGFR (OR: 0.86, 95%CI: 0.73–1.02, $p = 0.09$), or baseline sCR values (OR: 3.48, 95%CI: 0.20–61.1, $p = 0.39$). In the bivariable models, the relationship between study arm and PC-AKI remained consistent after controlling for these unbalanced factors (OR: 0.63–0.94) (Table 4).

Table 1 Patient and clinical characteristics

		All patients	Oral hydration	i.v. hydration	p-value
Patients		174	82 (47.1)	92 (52.9)	
Age, years	Median (range)	75 (35–90)	73 (35–90)	76 (58–81)	**0.032**
Gender	Male	119 (68.4)	57 (69.5)	62 (67.4)	0.87
	Female	55 (31.6)	25 (30.5)	30 (32.6)	
Associated risk factors					
Diabetes mellitus		74 (42.5)	32 (39)	42 (45.7)	0.44
Arterial hypertension		124 (71.3)	53 (64.6)	71 (77.2)	0.09
Cardiovascular disease		54 (31)	21 (25.6)	33 (35.9)	0.19
Non-oncological nephrotoxic medications					
RAS inhibitors		113 (64.9)	53 (64.6)	60 (65.2)	> 0.95
ACE-i		46 (26.4)	15 (18.3)	31 (33.7)	
AIIRA		27 (15.5)	18 (21.9)	9 (9.9)	
Diuretics					
Loop diuretics		26 (14.9)	12 (14.6)	14 (15.2)	
Thiazides diuretics		10 (5.7)	7 (8.4)	3 (3.3)	
Potassium-sparing diuretics		2 (1.2)	0 (0)	2 (2.2)	
NSAIDs		4 (2.3)	3 (3.6)	1 (1.1)	
Antivirals		1 (0.6)	0 (0)	1 (1.1)	
Laboratory values					
Baseline eGFR	Median (range)	37.0 (25.0–46.0)	39.0 (28.0–46.0)	36.0 (25.0–44.0)	**< .001**
eGFR 48 h post-CT	Median (range)	37.5 (21.0–63.0)	39.5 (21.0–58.0)	36.0 (23.0–63.0)	**< .001**
eGFR difference from baseline	Median (range)	0.0 (− 11.0–28.0)	0.0 (− 11.0–15.0)	0.0 (− 9.0–28.0)	0.09
Baseline ssCR	Median (range)	1.7 (1.2–2.2)	1.6 (1.2–2.2)	1.7 (1.2–2.2)	0.07
sCR 48 h post-CT	Median (range)	1.7 (1.0–2.7)	1.6 (1.0–2.7)	1.7 (1.1–2.5)	**0.013**
sCR difference from baseline	Median (range)	0.0 (− 0.8–0.7)	− 0.0 (− 0.4–0.7)	0.0 (− 0.8–0.5)	0.056

i.v., intravenous; *CT*, computed tomography; *eGFR*, estimated glomerular filtration rate; *sCR*, serum creatinine; *ACE-i*, angiotensin-converting enzyme inhibitors; *AIIRA*, angiotensin II receptor antagonists; *NSAIDs*, nonsteroidal anti-inflammatory drugs

Numbers in () represent frequency with percent of column total unless otherwise stated

Discussion

This retrospective analysis of the data acquired during the NICIR study demonstrates that oral hydration was as effective as i.v. hydration in the prophylaxis of PC-AKI after CE-CT in the oncologic subgroup of patients with IIIb CKD of this trial. In this subgroup, the overall PC-AKI rate was 4.6% (8 patients), with 3.7% (3 patients) in the oral hydration arm and 5.4% (5 patients) in the i.v. hydration arm.

It is important to emphasise that most patients included in this oncological subgroup of the NICIR study sample were elderly patients with multiple risk factors for AKI, as shown in Table 1. In addition, abdominal tumours were particularly prevalent in our sample (76.9%), specifically urinary tumours (51.1%) (Table 2). One explanation for this circumstance could be that most of these tumours and their curative treatment (surgery, targeted radiotherapy, and chemotherapy) tend to have an impact on renal function. Note that the four cases in our sample that presented irreversible PC-AKI were patients over 70 years of age with multiple associated risk factors for the development of AKI, regardless of iodinated contrast administration and method of prophylaxis, as shown in Fig. 1. As mentioned previously, the development of AKI is usually a multifactorial process. These factors are more present in oncologic patients, which exponentially increases the risk of renal toxicity in this population [4, 5]. Therefore, all cancer patients should be considered as a high-risk population for developing AKI and should be explicitly protected with prophylactic measures to avoid PC-AKI.

Some studies describe subclinical damage with reduction in the functional reserve of the kidneys in patients receiving multiple doses of iodinated contrast over an extended period of time, and this reduction in functional reserve does not translate into analytical alterations until it is well established

Table 2 Oncological characteristics

	All patients	Oral hydration	i.v. hydration
Patients	174	82 (47.1)	92 (52.9)
Tumour type			
Urological	89 (51.1)	40 (48.8)	49 (53.3)
Gynaecological	3 (1.7)	3 (1.7)	0 (0.0)
Gastrointestinal	42 (24.1)	16 (20.7)	26 (28.3)
Lung	15 (8.6)	8 (9.8)	7 (7.6)
Breast	4 (2.3)	2 (2.4)	2 (2.2)
Others	21 (12.1)	16 (19.5)	5 (5.4)
Active oncological treatment	23 (13.2)	15 (18.3)	8 (8.7)
Active nephrotoxic oncological treatment	12 (6.9)	7 (8.5)	5 (5.4)
Cytotoxic agents			
Carboplatin	1 (0.58)	0 (0)	1 (1.1)
Gemcitabine	1 (0.58)	1 (1.2)	0 (0)
Targeted therapies			
Interferon-alpha 2A	1 (0.58)	1 (1.2)	0 (0)
Lenalidomide	1 (0.58)	1 (1.2)	0 (0)
Pembrolizumab (PD-1 inhibitor)	5 (2.9)	1 (1.2)	4 (4.4)
Atezolizumab (PDL-1 inhibitor)	1 (0.58)	1 (1.2)	0 (0)
Cetuximab (EGFR inhibitor)	1 (0.58)	1 (1.2)	0 (0)

PD-1, programmed cell death protein-1; *PDL-1*, programmed death-ligand 1; *VEGFR*, vascular endothelial growth factor; *EGFR*, epidermal growth factor receptor

Numbers in () represent frequency with percent of column total unless otherwise is stated

[17]. Unfortunately, we currently do not have clinical parameters such as renal functional reserve stress tests or urinary markers to assess any eventual hidden renal damage. In this regard, the European Society of Urogenital Radiation (ESUR) guidelines recommend delaying repeated exposure of iodinated contrast media for 48 h in patients with pre-existing CKD [18]. The European Renal Best Practice guidelines recommend that if AKI develops after contrast administration, repeat exposure should preferably be delayed until the sCR level has returned to baseline values [19]. Although a short time span between chemotherapy administration and CE-CT increases the risk of AKI [20], as far as we know, no study has specifically addressed evaluation of the risk of nephrotoxicity in patients with cancer on active treatment undergoing serial CE-CT, especially in patients on clinical trials that usually undergo repeated CE-CT with a short time period [21].

In our study, we used hypo-osmolar non-ionic iodinated contrast media, which has a higher osmolarity than plasma [6, 22]. There is controversy in the literature as the type of contrast to use in oncologic patients in order to preserve renal function. Some authors propose the use of iso-osmolar contrast in these patients, as it is less harmful to the kidney [23]. However, most radiological and clinical guidelines consider that this protection is not proven, especially when the route of administration is intravenous [11, 20, 24]. Werner et al. published the first series investigating the incidence of PC-AKI with elective CE-CT in oncologic patients with CKD IIIb receiving oral hydration prophylaxis and iso-osmolar contrast, and reported 4.2% of patients developing PC-AKI [25]. These results are similar to those of our series in the oral hydration study arm, using hypo-osmolar iodinated contrast media (3.7%). Prospective randomised studies are needed to compare the two types of contrast in order to determine whether there are significant differences between hypo-osmolar and iso-osmolar non-ionic contrast media regarding renal function protection.

Based on two trials (AMAZING, Kompas), the threshold for prophylactic i.v. hydration after i.v. injection of iodinated contrast media has recently been reduced from 45 to 30 mL/min/m^2 in most radiological guidelines [11, 26, 27]. However, other clinical and radiological societies advocate that there is not enough evidence to lower this threshold [28]. Specifically, the Cosmai et al. white paper consensus publication in patients with cancer advises hydrating all oncologic patients with an eGFR less than 60 mL/min/m^2 before CE-CT [20]. Although studies on oral hydration are limited, preliminary evidence on this strategy suggests that it is as safe and effective as intravenous prophylaxis [13, 29]. Furthermore, this evidence suggests the alternative of performing a more straightforward and cheaper regimen for these patients, which we already perform in our hospital in all patients undergoing an elective CE-CT [12].

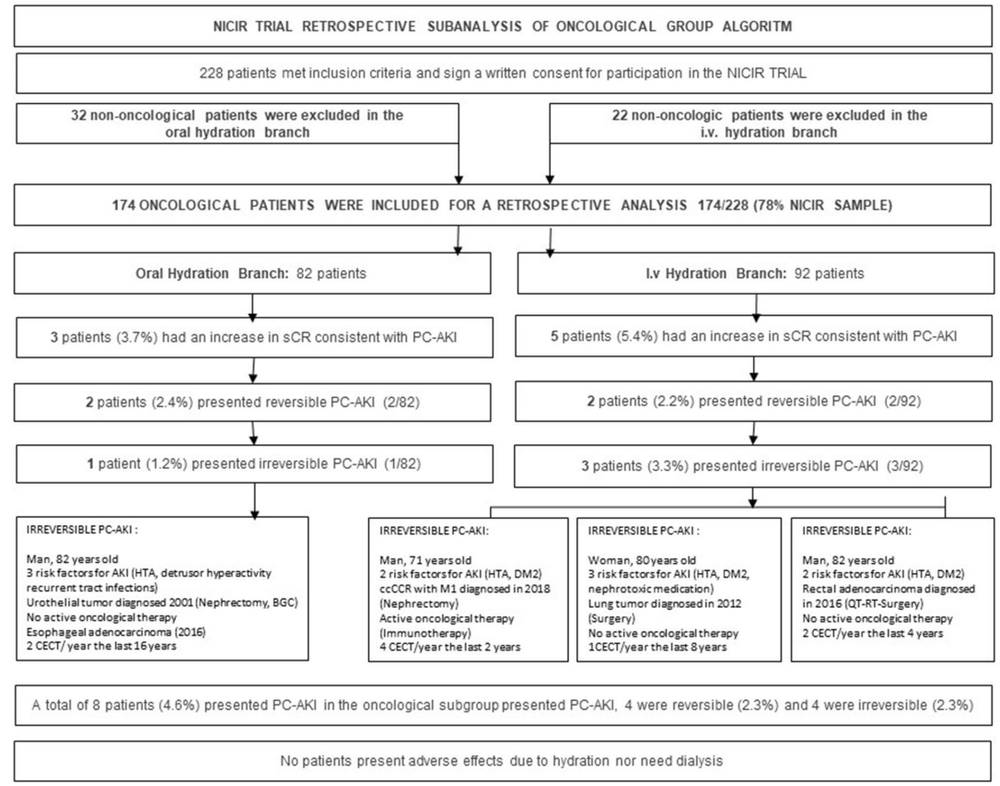

Fig. 1 NICIR trial retrospective subanalysis of oncological group algorithm

Table 3 PC-AKI rates

		Oral hydration		i.v. hydration	
		% (95%CI)	N	% (95%CI)	N
PC-AKI	Yes	3.7% (0.8–10.3%)	3/82	5.4% (1.8–12.2%)	5/92
Reversible PC-AKI	Irreversible	1.2% (0.0–6.6%)	1/82	3.3% (0.7–9.2%)	3/92
	Reversible	2.4% (0.3–8.5%)	2/82	2.2% (0.3–7.6%)	2/92

PC-AKI, post-contrast acute kidney injury; *i.v.*, intravenous

Dehydration is common in oncologic patients due to many factors associated with cancer itself and its treatment [23]. It is well established that dehydration is also a risk factor for PC-AKI. Prolonged fasting of liquids and solids usually performed before CE-CT is, in itself, a risk factor for developing PC-AKI due to the dehydration to which the patient is subjected [30]. Prolonged fasting can also amplify the stress response of patients and even cause anxiety, non-cooperation, weakness, hypoglycaemia, a decline in blood pressure, and severe shock reactions, especially in older cancer patients [30, 31]. In addition, patients often stop taking routine medication during fasting, which may increase the health risk for patients with hypertension or diabetes or those who require continuous medications. Recent articles published in the literature demonstrated that fasting of solid food and fluids before injection of iodinated contrast media is not needed, and specifically ingestion of clear inert fluid less than 1 h before CE-CT rarely induced nausea and

Table 4 Associations with PC-AKI controlling for unbalanced baseline factors

	Univariable			Bivariable: sCR			Bivariable: eGFR			Bivariable: age		
	OR	(95%CI)	*p*-value	OR	(95%CI)	*p*-value	OR	(95%CI)	*p*-value	OR	(95%CI)	*p*-value
Arm												
Oral	0.66	(0.15–2.86)	0.58	0.72	(0.16–3.17)	0.67	0.94	(0.20–4.34)	0.94	0.63	(0.14–2.81)	0.55
i.v	REF			—			—			—		
Baseline sCR	3.48	(0.20–61.09)	0.39	3.16	(0.17–57.37)	0.44	—			—		
Baseline eGFR	0.86	(0.73–1.02)	0.09	—			0.87	(0.73–1.03)	0.10	—		
Age, years	0.99	(0.94–1.06)	0.85	—			—			0.99	(0.93–1.06)	0.76

PC-AKI, post-contrast acute kidney injury; *i.v.*, intravenous; *sCR*, serum creatinine; *eGFR*, estimated glomerular filtration rate

vomiting and never aspiration [32–34]. Barbosa et al. specifically studied this in cancer patients and reported no clinically or statistically significant differences in the frequency of adverse reactions in outpatients with cancer undergoing CE-CT with or without preparative fasting [30]. The latest ESUR guidelines (10.0) clear state that fasting and interruption of medication are not recommended before the administration of lhypo- or isosmolar iodinated contrast media [18]. In our institution, the traditional fasting policy prior to CE-CT has been abolished according to this new statement in all outpatients, unless required for certain types of imaging tests.

One limitation of our series is that few patients were undergoing active oncological treatment at the time of the NICIR study and even fewer were receiving nephrotoxic oncological treatment. Therefore, our results may not be directly applicable to patients with active oncological treatment. Another significant limitation of this study is that our series corresponds to a retrospective assessment of the NICIR trial. Furthermore, our sample size was small and with this small sample size and limited number of events, the power to detect a true difference is low. However, it should be noted that considering that we studied oncological patients with multiple associated risk factors and confined to a subgroup of patients with severe CKD, the incidence of PC-AKI in our study was not higher than that reported in the literature for groups with far fewer risk factors [25].

Conclusion

Our study demonstrates the safety and efficacy of oral hydration in the prevention of PC-AKI in oncology patients These results justify the use of oral hydration in oncological patients with stage IIIb CKD undergoing elective CE-CT, until there is scientific consensus on whether or not prophylactic hydration should be performed in this subgroup of CKD patients. However, this is a retrospective study with relative small numbers, and prospective randomitzed trial in this subgroup of patients with sufficient power to show non-inferiority is needed to draw definitive conclusions in this regard.

Abbreviations i.v.: Intravenous; CT: Computed tomography; CE-CT: Contrast-enhanced CT; PC-AKI: Post-contrast acute kidney injury; sCR: Serum creatinine; CKD: Chronic kidney disease; AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate; ESUR: European Society of Urogenital Radiology

Author contribution CS, JAA, CN, and LO contributed to the concept and design of the study and contributed critical revision of the manuscript. CS, EG, and AP were responsible for the data analysis. CS, AP, and AdF were responsible for interpretation of results and drafting the masnuscript. All authors read and approved the final manuscript.

Availability of data and materials The analyzable dataset is available from the authors upon reasonable request, and with permission of Hospital Clinic de Barcelona database.

Code availability Not applicable.

Declarations

Ethics approval All data used to perform this retrospective analysis were de-identified. This retrospective study was approved by the Institutional Review Board and the Ethical Committee of our institution (HCB/2021/0021). Signed consent was not needed for this retrospective analysis.

Consent to participate Not applicable.

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Competing interests The authors declare no competing interests.

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DISCUSSIÓ

6. DISCUSSIÓ

L'anàlisi prospectiva de l'estudi NICIR i l'anàlisi retrospectiva del subgrup de pacients oncològics demostra que la hidratació via oral no és inferior a la hidratació via i.v. com a mesura profilàctica de la LRA-PC quan es realitza una TC amb contrast iodat en pacients amb IRC IIIb. Els resultats del nostre estudi mostren una taxa més baixa de LRA-PC al braç d'hidratació oral, 4,4% a l'estudi NICIR i 3,7% a la subanàlisi de pacients oncològics, comparant-la a la del braç d'hidratació i.v., 5,3% a l'estudi NICIR i 5.4% a la subanàlisi de pacients oncològics. Aquestes taxes de LRA-PC realitzant la profilaxi amb hidratació via oral són comparables a les publicades en estudis previs amb esquemes d'hidratació i.v., com els de la sèrie de Kooiman et al. que mostra taxes d'incidència entre 3% i 4.1% amb una pauta de hidratació i.v. amb bicarbonat una hora abans de la TC (30). Crec que és important destacar que la pauta del grup de Kooiman et al. és actualment la pauta recomanada a les noves guies ESUR 10.0 (23). La ràtio de LRA-PC no reversible va ser de 1.8% (95%CI: 0.2-6.2%) a les dues branques de l'estudi NICIR. Amb aquests resultats podem concloure que la hipòtesi de la nostra tesi, —és a dir, la no inferioritat de la hidratació per via oral envers la hidratació i.v. com a forma efectiva de profilaxi de la LRA-PC— ha quedat demostrada.

Cal remarcar que cap pacient de l'estudi NICIR va requerir diàlisi un més després de la TC amb contrast ni va presentar esdeveniments adversos secundaris a cap dels dos règims d'hidratació emprats. Per tant, també podem afirmar que la hidratació oral és una forma profilaxi de la LRA-PC efectiva i segura, complint els objectius secundaris primer, segon i tercer d'aquesta tesi.

La fisiopatogènia de la LRA-PC està relacionada amb el dany directe causat pel contrast iodat a les cèl·lules epitelials i endotelials, seguit de la inflamació, l'estrès oxidatiu, l'augment de la càrrega osmòtica i, finalment, la hipoperfusió i la hipòxia renal. Teòricament, tant la hidratació i.v. com la hidratació oral haurien de protegir de forma similar envers la LRA-PC millorant el flux sanguini renal i augmentant el filtrat renal, i d'aquesta manera minimitzar l'exposició de cèl·lules epitelials i endotelials al contrast, disminuir la viscositat de l'orina, prevenir l'obstrucció tubular i agilitzar l'eliminació dels mitjans de contrast (7,11). La hidratació oral, addicionalment, acceleraria l'excreció d'aigua pel ronyó mitjançant mecanismes osmoreguladors, de manera que l'acció fisiològica de la hidratació oral, en suprimir l'alliberament de vasopressina, conduiria

a un ràpid augment de la diüresi i, per tant, proporcionaria una important protecció renal a curt termini (40).

Les metaanàlisis publicades suggereixen que la hidratació oral podria ser tan eficaç com la hidratació i.v. en la prevenció de PC-AKI (41-43). Analitzant les sèries dels estudis inclosos en aquestes metaanàlisis evidenciem que els estudis mostren una heterogeneïtat significativa en molts paràmetres:

1. Tracten diversos tipus de procediments en un mateix estudi (cateterisme cardíac, TC amb contrast, etc.).

2. La immensa majoria analitzen l'eficàcia de la hidratació oral en procediments cardiovasculars amb injecció de contrast per via arterial.

3. Barregen contrast iònic i no iònic, i diferents vies d'administració (arterial i intravenosa). Recordem que actualment, el contrast iodat iònic no s'utilitza a causa de la seva elevada nefrotoxicitat, cosa que podria afectar les conclusions generals de les primeres metaanàlisis que incloïen estudis realitzats amb contrast iònic, com és el cas de la sèries de Taylor et al. del 1998, la de Trivedi et al. del 2003 i la d'Angoulvant et al. del 2009 (44-46).

4. La majoria dels pacients inclosos en aquests estudis presenten una funció renal normal o una alteració de la funció renal lleu.

5. Els protocols de profilaxi d'hidratació per via oral varien àmpliament d'un estudi a un altre, i en alguns estudis ni tan sols existeix un protocol estandarditzat. Fins el 2010, l'únic estudi en el que la hidratació i.v. té millors resultats que la hidratació oral es el de Trivedi et al. del 2003, on no s'estableix una pauta clara de hidratació oral, convidant únicament al pacient a beure molt (45).

6. Per altra banda, els assajos clínics prospectius randomitzats inclouen un nombre molt petit de pacients. La sèrie més llarga de les publicades és la de Akyuz et al. del 2014, amb 225 pacients amb funció renal normal als que es practica una coronariografia (47).

A les figures 11 i 12 podem veure les característiques dels estudis que comparen la hidratació oral i la i.v. publicats fins el moment, extretes dels articles de Hiremath i Song (43,48).

Table 1. Clinical Setting and Hydration Protocols of Included Trials.

Study (year)	Contrast Procedure	Contrast Type	Intravenous Regimen	Oral Regimen	Study Definition of CI-AKI
Taylor (1998)	cardiac catheterization	Ionic (74%) Nonionic (24%)	0.45% saline 75 mL/hour for 12 hours before and 12 hours after	1000 mL water over 10 hours before and IV 0.45% saline after for 6 hours	Increase in creatinine from baseline of at least 26.4 μmol/L (0.3 mg/dl) within 48 hours
Trivedi (2003)	nonemergency cardiac catheterization	Low-osmolality, Ionic	1 mL/kg/hour of isotonic saline for 12 hours before	Allowed unrestricted oral fluids	Increase in creatinine from baseline of at least 44.2 μmol/L (0.5 mg/dl) within 48 hours
Dussol (2006)	various radiological procedures	Low-osmolality, Non-ionic	15 mL/kg isotonic saline over 6 hours before	1 g/10 kg body weight NaCl for 2 days before	Increase in creatinine from baseline of at least 44 μmol/L (0.5 mg/dl) within 48 hours
Lawlor (2007)	elective, outpatient angiography	NR*	1 mL/kg/hour isotonic saline 12 hours before and 12 hours after	1000 mL water over 12 hours before and IV saline 1 mL/kg/hour for 12 hours post	Increase in creatinine from baseline of at least 25% or 44 μmol/L (0.5 mg/dl) at 48 hours
Cho (2010)	elective coronary angiogram	Low-osmolality, Non-ionic (isoversol)	3 mL/kg bolus of isotonic saline or sodium bicarbonate 1 hour before and 1 mL/kg/hour for 6 hours post	500 mL water 4 hours before, stopped 2 hours before; 3.9 g oral $NaHCO_3$ 20 minutes before; 600 mL of water post procedure with 1.95 g $NaHCO_3$ at 2 and 4 hours or 500 mL water 4 hours before, stopped 2 hours before and 600 mL of water post procedure	Increase in creatinine from baseline of at least 25% or 44 μmol/L (0.5 mg/dl) at 72 hours
Wrobel (2010)	percutaneous coronary intervention	Low-osmolality, Non-ionic (isoversol)	Isotonic saline, 1 mL/kg/hour for 6 hours before and 12 hours after	Oral mineral water 1 mL/kg/hour for 6–12 hours before and 12 hours after	Increase in creatinine from baseline of at least 25% or 44 μmol/L (0.5 mg/dl) at 72 hours

*NR, not reported; NaCl, sodium chloride; $NaHCO_3$, sodium bicarbonate.
Note: Conversion factors for units: serum creatinine in mg/dL to mol/L, ×88.4.
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Figura 11: Tabla que llista les característiques dels estudis que comparen l'eficacia de la hidratació oral i la i.v. extreta de la metanàlisi de Hiremath et al del 2013 (43).

Figura 12: Tabla que llista les característiques dels estudis que comparen l'eficacia de la hidratació oral i la i.v., extreta de l'article de Song et al. del 2019 (48).

Table 1 Characteristics of randomized controlled trials with intervention of oral hydration among patients undergoing coronary angiography/percutaneous coronary intervention

Study	Year	Sample size	Procedure	Contrast agent	Kidney function of participants	Contrast-induced nephropathy definition	Intervention protocols	
							Regimen one	Regimen two
Wrobel et al. [24]	2010	102	Elective CAG/PCI	Low osmolality, non-ionic (isoverol)	CKD and diabetes mellitus	> 44.2 μmol/L (> 0.5 mg/dL) absolute increase or a > 25% relative increase in serum creatinine within 72 h of contrast exposure	Oral mineral water 1 mL/kg/h for 6–12 h before and 12 h after contrast exposure	Isotonic saline, IV, 1 mL/kg/h for 6 h before and 12 h after contrast exposure (reduced to 50% in patients with CHF)
Kong et al. [26]	2012	120	Elective CAG	Low osmolality, ionic (iopromide)	Normal renal function	> 44.2 μmol/L (> 0.5 mg/dL) absolute increase or a > 25% relative increase in serum creatinine within 48–72 h of contrast exposure	Oral 2000 mL neutral water within 24 h after and/or 500 mL water before contrast exposure	Isotonic saline, IV, 1 mL/kg/h for 12 h before and 24 h after contrast exposure
Akyuz et al. [12]	2014	225	Elective CAG	Non-ionic low osmolar iopromide, Ultravist	At least one of the high-risk factors for developing CI-AKI (advanced age, type 2 diabetes mellitus, anemia, hyperuricemia, a history of cardiac failure or systolic dysfunction), eGFR ≥ 60 mL/min)	> 44.2 μmol/L (> 0.5 mg/dL) absolute increase or a > 25% relative increase in serum creatinine within 48 h of contrast exposure	Drink neutral water as much as possible for 12 h before and 2 h after contrast exposure	Isotonic saline, IV, 1 mL/kg/h for 12 h before and 12 h after contrast exposure
Cho et al. [25]	2010	91	Elective CAG	Low osmolality, non-ionic (isoverol)	CKD (baseline creatinine at least 1.1 md/dL or eGFR < 60 mL/min)	> 44.2 μmol/L (> 0.5 mg/dL) absolute increase or a > 25% relative increase in serum creatinine within 72 h of contrast exposure	Water; 500 mL started 4 h prior and stopped 2 h prior to procedure followed by oral hydration with 600 mL of water post-procedure	Isotonic saline or sodium bicarbonate solution, IV, 3 mL/kg/h for 1 h before and 6 h after contrast exposure (for patients greater than 110 kg, infusion rates will be based on that for a 110 kg person
Angoulvant et al. [30]	2009	201	Elective CAG	Ionic low osmolar (Hexabrix)	Serum creatinine < 140 μmol/L	The change in calculated creatinine clearance in 24 h and 3 days	1000 mL isotonic saline, IV, during and oral 2000 mL tap water within 24 h after contrast exposure	Oral 2000 mL tap water within 24 h after contrast exposure
Taylor et al. [21]	1998	36	Elective cardiac catheterization	Ionic contrast media in most cases	Renal dysfunction (serum creatinine ≥ 1.4 mg/dL)	An increase in creatinine of ≥ 0.5 mg/dL within 48 h of contrast exposure	Oral 1000 mL water over 10 h before then 0.45% saline, IV, 300 mL/h during and 6 h after contrast exposure	0.45% saline, IV, 75 mL/h for 12 h before and 12 h after contrast exposure

CAG coronary angiography, *CHF* congestive heart failure, *CI-AKI* contrast-induced acute kidney injury, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *IV* intravenous, *PCI* percutaneous coronary intervention

Fins el moment d'escriure aquesta tesi, el nostre estudi NICIR és l'únic estudi publicat que compara la hidratació oral amb la hidratació i.v. com a forma de profilaxi de la LRA-PC en pacients als que es realitza un estudi de TC amb contrast iodat injectat per via i.v. de forma prospectiva i randomitzada. El nostre estudi avalua pacients als que se'ls hi realitza un únic procediment (TC amb contrast), amb contrast injectat per una sola via (i.v.), amb una alteració de la funció renal de moderada a severa (estadi IIIb de KDIGO), i en pacients únicament ambulatoris (no es barregen pacients ambulatoris i ingressats). Revisant tota la literatura publicada sobre l'eficàcia de la hidratació oral, que es basa fonamentalment en estudis cardiovasculars amb injecció de contrast per via arterial, trobem només dos estudis sobre l'eficàcia de la hidratació oral en pacients als que es realitza una TC amb contrast iodat, i ambdós presenten problemes metodològics per arribar a conclusions robustes sobre la no inferioritat de la hidratació oral versus la hidratació i.v.:

- La sèrie de Dussol et al. del 2006 inclou altres procediments radiològics diferents de la TC (49).

- La sèrie de Garcia-Ruiz et al. del 2004 no disposa de grup control amb hidratació i.v. (50).

En l'estudi NICIR la pauta d'hidratació oral consisteix en beure 500 ml d'aigua dues hores abans de la TC i 2000 ml d'aigua durant les 24 hores després de la TC. Tots els pacients que no varen fer la pauta d'hidratació oral complerta abans i després de l'estudi TC van ser rebutjats. El fet que la pauta d'hidratació oral es realitzi fora de l'hospital fa que sigui més difícil controlar que es faci correctament. Song et al., en el seu estudi, demostren que la LRA-PC augmenta de manera exponencial si els pacients realitzen la hidratació per via oral de forma no reglada i/o incomplerta (51). Per això és molt important que en la pràctica clínica es donin les indicacions precises perquè el pacient sàpigui perfectament com ha de realitzar la pauta d'hidratació oral i la compleixi. En el nostre estudi es va utilitzar aigua sense gas que podia ser de l'aixeta o embotellada. Així s'ha fet a la resta d'estudis publicats, tret del de Wróbel —que utilitza aigua mineral— obtenint també una bona protecció de la LRA-PC (52).

Volem destacar que a la sèrie que conforma el nostre estudi els pacients, a més de la IRC grau IIIb, presenten molts altres factors de risc associats a la nefropatia: edat avançada, diabetis, malaltia cardiovascular, hipertensió arterial i —com comentarem al proper paràgraf— un 74% són pacients oncològics (174 dels 228 pacients de l'estudi NICIR) (5). Això és especialment important perquè el nostre estudi posa sobre la taula una solució barata i d'implementació fàcil davant el debat obert a la comunitat mèdica sobre el fet que les societats radiològiques ESUR i ACR hagin desestimat aquests factors de risc i s'hagi baixat el llindar de profilaxi després de la injecció de contrast iodat per via i.v. a FG menors de 30 ml/min/1.73m^2, sense excepcions i sense tenir en compte la labilitat renal d'aquests pacients (2,12,23). L'estudi NICIR demostra que la hidratació oral és igual d'efectiva que la hidratació i.v. en pacients que presenten múltiples factors de risc per presentar IRA i pot optar-se per la hidratació oral com a forma de profilaxi en pacients d'alt risc amb FG majors de 30 ml/min/1.73m^2, que d'altra manera, seguint les noves guies radiològiques, quedarien desprotegits en quedar exempts de qualsevol tipus d'hidratació profilàctica.

Els pacients oncològics són pacients d'especial risc per a desenvolupar una LRA-PC a l'associar la realització de moltes proves amb contrast iodat amb múltiples factors concomitants que poden empitjorar la funció renal, tal com detallem a la introducció. Per això, quan vam veure que un 74% dels pacients de l'estudi NICIR eren pacients oncològics vam voler analitzar-los específicament. En aquest subgrup de pacients vam analitzar característiques específiques dels pacients oncològics: el tipus de tumor, el tractament, si estaven en tractament actiu en el moment de realitzar la TC i si aquest tractament que rebien era nefrotòxic.

La majoria dels pacients inclosos en aquest subgrup oncològic de la mostra de l'estudi NICIR també són pacients d'edat avançada amb múltiples factors de risc per desenvolupar nefropatia, tal com es mostra a les taules descriuen les característiques de la mostra del segon article que composa aquesta tesi (6). Crida l'atenció que els tumors abdominals són especialment prevalents a la nostra sèrie (76,9%), i ho són específicament els tumors renals o de la via urinària (51,1%). Una explicació d'aquesta destacada incidència podria ser que la majoria d'aquests tumors i el seu tractament (cirurgia, radioteràpia, quimioteràpia o teràpies dirigides) tenen un impacte directe en el ronyó i la via urinària, per la qual cosa considerem que han de tractar-se amb

especial cura. En la nostra sèrie retrospectiva del subgrup de pacients oncològics els quatre casos que van presentar LRA-PC irreversible eren pacients majors de 70 anys i amb múltiples factors de risc associats a la nefropatia, independentment de l'administració de contrast iodat i del mètode de profilaxi. El desenvolupament de la IRA sol ser un procés multifactorial i els pacients oncològics presenten molts d'aquests factors de risc de forma concomitant. Per tant, tots els pacients amb càncer s'han de considerar com una població d'alt risc per desenvolupar IRA i creiem que han de ser explícitament protegits amb mesures profilàctiques per evitar la LRA-PC. El fet que la hidratació per via oral no sigui inferior a la hidratació i.v. és una opció que aquesta tesi posa sobre la taula pels pacients oncològics i que fins i tot es pot universalitzar, com hem fet a l'Hospital Clínic.

Alguns autors defensen que existeixen danys subclínics renals associats a l'administració continuada de contrast iodat que no es tradueixen en alteracions analítiques fins molt avançada la noxa per la capacitat compensatòria de la reserva funcional renal (40). Malauradament, actualment no disposem de paràmetres clínics —com ara proves d'estrès de reserva funcional renal o marcadors urinaris— per avaluar qualsevol eventual dany renal ocult (21). En aquest sentit, les directrius de l'ESUR recomanen retardar l'exposició repetida a mitjans de contrast iodats fins a 48 hores en pacients amb IRC preexistent i les guies europees de bones pràctiques renals recomanen que —si el pacient desenvolupa una LRA-PC després de l'administració de contrast iodat— es retardi la nova exposició al contrast iodat fins que el nivell de Cr hagi tornat als valors basals sempre que sigui possible (23,53). L'European Society of Medical Oncology (ESMO), per la seva part, recomana que es deixi passar un període mínim de temps entre l'administració del tractament oncològic i la TC amb contrast per disminuir el risc de LRA-PC (54). Fins el moment cap estudi ha abordat específicament el risc de nefropatia associada al contrast a llarg termini, com passa en pacients amb càncer en tractament actiu sotmesos a TC amb contrast repetits de 5 a 10 anys. Pel que fa a aquest punt, és important ressaltar que en els pacients oncològics inclosos en assaigs clínics les TC amb contrast es programen encara més sovint durant tot el tractament i control evolutiu (11).

En el nostre estudi vam utilitzar un mitjà de contrast iodat no iònic dels anomenats hipoosmolars, tot i que, com hem comentat, presenten una osmolaritat més alta que

el plasma (8). Alguns autors proposen l'ús del contrast isoosmolar en pacients oncològics, afirmant que és menys nociu per al ronyó (21). Basant-se en les metaànalisis publicades, les darreres guies radiològiques consideren que aquesta major protecció del contrast isoosmolar sobre el hipoosmolar no està provada quan la via d'administració del contrast iodat és per via i.v., si bé es cert que en l'última actualització de les guies clíniques de la ESMO es recomana el contrast isoosmolar en pacients oncològics d'alt risc (54). Werner et al. van publicar la primera sèrie que investigava la incidència de LRA-PC amb TC amb contrast electiva en pacients oncològics amb ERC IIIb que rebien profilaxi d'hidratació oral i contrast isoosmolar, i van reportar que un 4,2% dels pacients desenvolupaven LRA-PC (55). La incidència de LRA-PC en el braç d'hidratació oral del subgrup de pacients oncològics del nostre estudi és d'un 3,7%. Aquests resultats recolzen que es puguin utilitzar indistintament contrasts no iònics isoosmolars o hipoosmolars per a la realització d'una TC amb contrast a un pacient oncològic, fins i tot utilitzant profilaxi per via oral.

Com ja hem explicat a la introducció, després de la publicació dels resultats dels estudis AMAZING i Kompas a les guies radiològiques més utilitzades, les de la ESUR i les de l'ACR, el llindar màxim de FG per indicar la hidratació profilàctica després de la injecció de mitjans de contrast iodats per via i.v. s'ha reduït de 45/min/1.73m^2 a 30ml/min/1.73m^2 (27-28). No obstant això, altres societats radiològiques i la majoria de societats clíniques defensen que no hi ha prou evidència per reduir aquest llindar (18). Concretament, Cosmai et al., a la publicació de consens de l'ESMO sobre els mecanismes de prevenció de la LRA-PC en pacients amb càncer, aconsella hidratar tots els pacients oncològics amb un FG inferior a 60ml/min/1.73m^2 abans de la TC amb contrast (54). Els resultats del nostre estudi ofereixen una solució fàcil i universalitzable que seria fer profilaxi en pacients oncològics amb un FG inferior a 60ml/min/1.73m^2 utilitzant la hidratació per via oral.

La deshidratació és un fenomen freqüent en pacients oncològics d'origen multifactorial (21). Està ben establert que la deshidratació també és un factor de risc per a la LRA-PC. El dejuni prolongat de líquids i sòlids que es realitza generalment abans de la TC amb contrast és, també, per si mateix, un factor de risc per desenvolupar LRA-PC a causa de la deshidratació a la que es sotmet al pacient abans de la prova (36). Per altra banda, el dejuni prolongat també pot amplificar la resposta a l'estrès dels pacients i

fins i tot provocar ansietat, falta de cooperació, debilitat, hipoglucèmia, disminució de la pressió arterial i reaccions de xoc greus, especialment en pacients amb càncer d'edat avançada i produir dany renal (30). A més, fins fa poc s'indicava als pacients que deixessin de prendre la medicació habitual pautada durant el dejuni preprova, cosa que pot augmentar el risc —per a la salut en general i pel ronyó en particular— dels pacients amb hipertensió o diabetis o, en general, dels que necessiten medicaments que no haurien de discontinuar-se. Articles recents publicats a la literatura han demostrat que no és necessari el dejuni de sòlids i líquids abans de la injecció de mitjans de contrast iodats, i, específicament, que la ingestió de líquids abans de la TC amb contrast rarament indueix a l'aparició de nàusees i vòmits i mai produeix aspiració pulmonar (37,38,56). Barbosa et al. ho van estudiar específicament en pacients amb càncer i no van trobar diferències clínicament o estadística significatives en la freqüència de reaccions adverses en pacients ambulatoris amb càncer sotmesos a TC amb contrast amb o sense dejuni preparatiu (36). La darrera guia ESUR 10.0 indica clarament que no es pauti dejuni ni s'interrompi cap medicació abans de l'administració de mitjans de contrast iodats hipo o isoosmolars (23). A la nostra institució s'ha abolit la política de dejuni tradicional anterior a la TC amb contrast en tots els pacients, tret que aquest dejuni sigui necessari per proves d'imatge de l'àrea abdominal que requereixin que l'estómac i l'intestí prim estiguin buits i/o la vesícula biliar plena. En aquests casos es pauta dejuni de sòlids, però en cap cas de líquids, que es segueixen administrant profusament abans i després de la prova i tampoc, en cap cas, es discontinua cap medicació.

Els resultats del nostre estudi demostren que la hidratació via oral es una estratègia de profilaxi vàlida pels pacients amb IRC de moderada a greu de la classificació de KDIGO, als que es realitza una TC amb contrast iodat. La hidratació oral és fàcil i còmoda pel pacient ambulatori que pot realitzar al seu domicili sense problemes. Quan es considera el cost, la hidratació oral és clarament l'opció preferible perquè no requereix ocupació hospitalària, a diferència de les pautes d'hidratació i.v. Actualment, la pauta profilàctica amb hidratació oral, tal com es descriu en aquest estudi, ja forma part de la guia clínica de profilaxi de la LRA-PC de tots els pacients ambulatoris als que se'ls hi realitzi un estudi amb contrast iodat de l'Hospital Clínic. L'única excepció per realitzar aquesta pauta d'hidratació oral és que el pacient tingui restringits els líquids. Al volant de citació de la prova radiològica amb contrast iodat s'indica específicament que no realitzi la pauta d'hidratació oral si té restringit els líquids, una indicació general que

ens es de molta ajuda perquè engloba tots els casos en que els pacients no poden beure líquids lliurement, i que són: la cirrosi amb ascites, la insuficiència cardíaca congestiva III-IV, la IRC terminal i la diàlisi.

A l'Hospital Clínic únicament realitzem la pauta d'hidratació i.v. als pacients que tenen un FG menor de 30ml/min/1.73m^2, seguint la guia ESUR 10.0. En pacients amb FG menor de 15ml/min/1.73m^2, és el nefròleg o el clínic responsable el que decideix si es pot o no administrar contrast iodat i la pauta d'hidratació i.v. es realitza a l'hospital de dia de nefrologia, en considerar-se pacients d'alt risc per presentar LRA-PC irreversible. Per últim, volem recalcar que tot pacient ingressat que estigui seguint qualsevol règim de serumteràpia es considera hidratat i en aquests casos no s'ha de retardar cap prova per realitzar hidratació profilàctica.

6.1. Limitacions dels estudis d'aquesta tesi doctoral

Aquest estudi té diverses limitacions:

1. Les taxes de LRA-PC van ser inferiors a les previstes en dissenyar la prova. En el disseny de la prova la incidència de la LRA-PC estimada a la branca d'hidratació i.v. va ser del 9%, basant-nos en estudis previs (41). No hem trobat cap causa aparent d'aquest resultat, que es pot deure a la selecció de mostres, a un seguiment més proper o, fins i tot, a l'atzar. El marge d'inferioritat del braç d'hidratació oral era igual al del control, cosa que indica que fins i tot el doble de la velocitat actual al braç d'hidratació i.v. es consideraria no inferior. L'estudi es va dur a terme a més de 200 pacients, mostrant taxes de LRA-PC del 4,4% (IC del 95%: 1,4-9,9%) al braç d'hidratació oral i del 5,3% (IC del 95%: 2,0-11,1%) al braç d'hidratació i.v. Per tant, atesa la taxa d'errors de tipus I del 5% unilateral, el límit superior del 90% del braç i.v. va ser del 10,2%, que va ser superior a la taxa observada del 4,4%, demostrant així la no inferioritat de la hidratació oral en comparació amb la hidratació i.v. sota els paràmetres establerts en el nostre estudi.

2. Tampoc no vam preveure diferències en els valors de laboratori basals entre els dos braços de l'estudi NICIR, cosa que va conduir a grups desequilibrats a causa de l'aleatorització no estratificada. Dit això, tot i que és possible que la no inferioritat demostrada en aquest estudi pugui ser una funció de confusió, sembla improbable que l'equilibri perfecte d'aquests grups produeixi una taxa superior al 9%. En els estudis futurs s'hauria de considerar l'ús de mostres aleatòries de blocs estratificats.

3. Tot i que la taxa de LRA-PC va caure dins del rang esperat, es trobava a l'extrem inferior, cosa que impedeix que tinguem una mida de mostra suficient per explorar completament els efectes/subgrups d'interacció potencial i de confusió. Els futurs estudis també haurien de tenir en compte la raresa de la LRA-PC, a més de les diferències entre grups.

4. També hem de considerar com una limitació d'aquest estudi el fet que les variacions naturals intrínseques en els nivells sèrics de la Cr fan que sigui difícil definir quines variacions són causades directament per l'administració de medi de contrast iodat i quines són senzillament secundàries a la fisiologia renal.

5. Una limitació significativa de l'estudi del subgrup oncològic és que es tracta d'una sèrie retrospectiva i la mida de la mostra és més petita que la del estudi NICIR. Tanmateix, cal assenyalar que tenint en compte que vam estudiar pacients oncològics amb múltiples factors de risc associats i, específicament, d'un subgrup de pacients amb IRC moderada/greu, la incidència de LRA-PC en el nostre estudi no va ser superior a la reportada a la literatura per a grups amb molts menys factors de risc sotmesos a hidratació i.v.

6. Una altra de les limitacions de la sèrie del subgrup oncològic és que pocs pacients estaven sotmesos a un tractament oncològic actiu en el moment de l'estudi NICIR i encara menys estaven rebent tractament oncològic nefrotòxic. Per tant, és possible que els nostres resultats de no inferioritat de la hidratació oral sobre la hidratació oral en pacients oncològics no siguin directament aplicables a pacients amb tractament oncològic actiu.

6.2. Beneficis esperats de la investigació, aplicabilitat i validesa d'aquesta tesi doctoral

La finalitat d'aquesta tesi ha estat proporcionar evidència científica de la no inferioritat de la hidratació oral com a forma de profilaxi de la LRA-PC sobre la hidratació i.v. en pacients ambulatoris amb IRC IIIb, als que es realitza una TC amb contrast. En aquest moment, tot i que les noves guies ESUR i ACR preconitzen no realitzar profilaxi en pacients amb FG major de 30 ml/min/1.73m^2, algunes societats radiològiques —i també les societats oncològiques i nefrològiques més importants— han plantejat la seva disconformitat amb aquest relaxament en la profilaxi de la LRA-PC i volen que es mantingui en FG major de 45 ml/min/1.73m^2 o fins i tot més alts si son pacients amb factors de risc, com per exemple els pacients oncològics. El nostre estudi demostra que en els pacients amb FG entre 45 i 30 ml/min/1.73m^2 la hidratació oral no es inferior a la hidratació i.v., per la qual cosa la hidratació oral pot convertir-se en una instrucció universal, que apareixi en tots els volants de citació, pel seu cost zero i per la manca d'efectes secundaris, com ja s'ha implementat a l'Hospital Clínic.

Amb la divulgació dels resultats obtinguts a la comunitat científica volem que es generalitzi la hidratació oral pre i postcontrast a nivell nacional i internacional, la qual cosa pot suposar una disminució important del cost hospitalari de la profilaxi de la LRA-PC a gran escala.

Per altra banda, la implicació en l'estudi NICIR del personal d'infermeria del CDI i específicament de la consulta d'infermeria de radiodiagnòstic, creada en principi per aquesta funció de prevenció de la LRA-PC, servirà per crear sinèrgies entre els diferents estaments del nostre institut per futurs assajos clínics.

Voldria acabar dient que aquesta tesi és el fruit del treball ingent de moltíssima gent des de fa més de 10 anys i que em sento tremendament orgullosa del camí recorregut per tot aquest equip, un camí que no ha estat fàcil i que s'ha materialitzat no només en aquests dos articles que ens posicionen com a capdavanters en el coneixement de la profilaxi de la LRA-PC amb hidratació via oral a nivell mundial sinó que hem aconseguit que es pugui oferir un tractament per la LRA-PC que millora la qualitat de vida dels nostres pacients, que disminueix la despesa sanitària i que dona una solució universalitzable a una de les qüestions probablement més problemàtiques a les que s'enfronten tots els serveis de radiodiagnòstic.

En l'apartat 9 d'aquesta tesi es detallen els documents, comunicacions, pòsters i publicacions que han generat aquesta tesi doctoral.

7

CONCLUSIONS

7. CONCLUSIONS

El nostre estudi demostra que la hidratació oral no es inferior a la hidratació intravenosa com a mesura profilàctica de la LRA-PC en pacients amb IRC IIIb als que se'ls hi realitza una TC amb contrast iodat, i específicament al subgrup de pacients oncològics d'aquest estudi.

La hidratació oral és un mètode profilàctic convenient i fàcil d'utilitzar en la prevenció de LRA-PC en pacients amb IRC en fase IIIb sotmesos a una TC amb contrast, afegint aquesta opció —com a alternativa d'hidratació universalitzable— al debat actual entre organitzacions radiològiques i clíniques sobre quin ha de ser el FG que s'utilitzi com a llindar de profilaxi per prevenir la LRA-PC quan s'injecta contrast per via i.v.

El nostre estudi NICIR no va tenir en compte la raresa de la LRA-PC i no va estratificar els grups. Els nous estudis prospectius randomitzats han de tenir en compte aquestes dues limitacions del nostre estudi, utilitzant mostres més grans i l'ús de mostres aleatòries de blocs estratificats.

8

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8. BIBLIOGRAFIA

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ARTICLES, COMUNICACIONS I PREMIS GENERATS PER AQUESTA TESI DOCTORAL

9. ARTICLES, COMUNICACIONS I PREMIS GENERATS PER AQUESTA TESI DOCTORAL

9.1. Articles

1. Sebastià C, Nicolau C, Martín de Francisco ÁL, Poch E, Oleaga L. Prophylaxis against postcontrast acute kidney injury (PC-AKI): updates in the ESUR guidelines 10.0 and critical review. Radiologia (Engl Ed). 2020 Jul-Aug;62(4):292-297. English, Spanish. doi: 10.1016/j.rx.2019.12.005. Epub 2020 Feb 3. PMID: 32029241

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Prophylaxis against postcontrast acute kidney injury (PC-AKI): Updates in the ESUR guidelines 10.0 and critical review☆

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Abstract The European Society of Urogenital Radiology (ESUR) updated its guidelines for prophylaxis against postcontrast acute kidney injury (PC-AKI) in 2018 (ESUR 10.0). These guidelines drastically reduce the indications for prophylaxis against PC-AKI after iodine-based contrast administration, lowering the cutoff for administering prophylaxis to glomerular filtration rates <30 ml/min/1.73 m^2 and eliminating most of the prior risk factors. Moreover, in cases where prophylaxis is considered necessary, the periods of hydration are shorter than in the previous version. These guidelines have been approved by most radiological societies, although they have also been criticised for excessive relaxation regarding risk factors, especially by the nephrological community. In this article, we critically review the changes to the guidelines.

PALABRAS CLAVE
Medios de Contraste;
Lesión renal aguda;
Tomografía computarizada;
Tasa de filtración glomerular;
Pautas de práctica como tema;
Factores de riesgo

Profilaxis de la lesión renal aguda poscontraste (LRA-PC). Actualización según la guía clínica ESUR 10.0 y revisión crítica

Resumen La European Society of Urogenital Radiology (ESUR) ha actualizado la guía de profilaxis de la lesión renal aguda poscontraste (LRA-PC) yodado en 2018, guía ESUR 10.0. Esta guía reduce drásticamente las indicaciones de la realización de la profilaxis de la LRA-PC yodado, rebajando el dintel de realización de profilaxis a filtrados glomerulares menores de 30 ml/min/1,73m^2 y eliminando la mayoría de los considerados factores de riesgo previamente. En los casos en que se considera necesario, las pautas de hidratación indicadas son más cortas que en la guía previa. Esta guía ha sido suscrita por la mayoría de las sociedades radiológicas,

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pero también ha sido criticada por su excesiva relajación en cuanto a los factores de riesgo, especialmente por la comunidad nefrológica. En este artículo revisamos los cambios que supone esta guía en relación con la anterior y planteamos las críticas a la misma.

Introduction

In 1980, the first case to relate the administration of iodinated contrast to the worsening of renal function was published.[1] Since 1999, this relationship has been known as contrast-induced nephropathy (CIN) and is defined as the worsening of renal function that occurs within 3 days after intravascular administration of the contrast medium, in the absence of an alternative aetiology, with an increase in the creatinine value of greater than 25% or 44 μmol/l (0.5 mg/dl).[2] There is an extensive bibliography on this subject that has been growing exponentially since the 80s. In general, the publications are very heterogeneous, which makes it difficult for us to establish a clear incidence of this entity, and very important variations are observed according to the methodology of each study.

In parallel, during recent decades, clinicians and especially radiologists have gone from total ignorance regarding the existence of CIN, injecting massive and repeated amounts of iodinated contrast in critically ill patients or those with acute renal failure (ARF) or chronic renal failure (CRF) in stage 4–5 (KDIGO classification),[3] to radical fundamentalism on this subject, not administering iodinated contrast even in patients with mild and moderate CRF in stage 2–3 (KDIGO classification), where its use can be of vital importance for diagnosis and patient management.

In 2008, Newhouse published an article in which he questioned the causality of iodinated contrast in CIN, demonstrating that there are spontaneous physiological variations of creatinine greater than 0.5 mg/dl that in many cases could be mistakenly attributed to the injection of iodinated contrast.[4] From that moment on many articles have appeared that address the true existence of CIN.[5] The 2014 McDonald study should be noted, in which it is demonstrated that creatinine variations after performing a computed tomography (CT) scan, with or without iodinated contrast, both in equivalent populations and at two different times in the same patient, do not show significant differences.[6]

At the same time, there are multiple CIN prophylaxis guidelines in the scientific literature that essentially use intravenous hydration as an effective method. Multiple medications are also postulated as nephroprotectors, the most commonly used one being N-acetylcysteine, although meta-analyses on this drug fail to demonstrate the superiority of N-acetylcysteine combined with hydration compared with hydration alone, so it is no longer recommended in the clinical reference guidelines of the European Society of Urogenital Radiology (ESUR) of 2014 (ESUR 9.0) or the American College of Radiologists of 2013.[7,8] Regarding the effectiveness of hydration as a prophylaxis of CIN, in 2017 the AMAZING study, published in *The Lancet*,[9] demonstrated that there is no inferiority in not performing hydration compared to performing it in patients with a glomerular filtration rate (GFR) greater than 30 ml/min. On the other hand, although the works in which the efficacy of oral hydration compared with intravenous hydration as a method of prophylaxis against CIN has been compared are scarce, in the latest meta-analysis performed it does not appear that oral hydration is inferior to intravenous hydration as a CIN protecting factor in both intraarterial and intravenous injection in patients with CRF 2–3 (KDIGO classification).[12]

Finally, it is important to note that recent publications have also shown that it is unnecessary to fast on liquids and solids for 6 hours before administering iodinated contrast, even inferring that preventing a patient from drinking for 4–6 h before the procedure may be a risk factor itself for kidney damage, due to the dehydration component involved.[10,11]

In this update article, we will review the new guidelines 10.0 of the ESUR's Contrast Media Safety Committee, which are collected in two articles published in *European Radiology* in 2018,[13,14] and on the ESUR website,[15] the changes compared to the previous 2014 guidelines,[7] their implications in clinical practice, and at the same time we will perform a critical review from the nephrological point of view.

Changes in ESUR guidelines 10.0 on prophylaxis against PC-AKI compared to the previous version, ESUR 9.0

This section highlights, in a grey box, the paragraphs taken from ESUR guidelines 10.0.[13–15] The summary of changes is shown in Table 1.

Definition

Post-contrast acute kidney injury (PC-AKI) is defined as an increase in serum creatinine ≥0.3 mg/dl or ≥1.5–1.9 times the baseline level within 48–72 h after intravascular administration of a contrast agent.

A baseline creatinine value is considered valid if obtained within seven days prior to the administration of contrast medium in patients with acute disease, acute deterioration of chronic disease, and any other adverse episode that can negatively influence renal function in hospitalised patients, and three months in other patients.[13,15]

Table 1 Differences between the ESUR 9.0 and ESUR 10.0 guidelines.

ESUR guidelines	ESUR 9.0 (2014)	ESUR 10.0 (2018)
Definition	CIN (Cr increase 0.5 mg/dl)	PC-AKI (Cr increase 0.3 mg/dl)
Prophylaxis threshold (GFR)	45 ml/min i.v./i.a.	30 ml/min i.v./i.a. second-pass 45 ml/min i.a. first-pass
Short hydration	1 h/6 h (up to 30 ml/min)	1 h (GFR between 30 and 15 ml/min i.v./i.a. second-pass)
Long hydration	6 h/6 h (GFR less than 30 ml/min)	1 h/4–6 h (GFR 45–15 ml/min i.a. first-pass)
NSAIDs	Suspended	Not suspended
Metformin	Suspended	Exceptionally suspended
Risk factors	Chronic or ARF, dehydration Repeated/high contrast medium doses Anaemia, HF, diabetes, nephrotoxic medication	Chronic or ARF, dehydration Repeated/high contrast medium doses

NSAIDs: nonsteroidal anti-inflammatory drugs; Cr: creatinine; GFR: glomerular filtration rate; h: hour; i.a.: intra-arterial; HF: heart failure; ARF: acute renal failure; i.v.: intravenous; PC-AKI: post-contrast acute kidney injury; CIN: contrast-induced nephropathy.

The deteriorating renal function that appears after the administration of iodinated contrast has gone from being called CIN to PC-AKI. In this new definition, the creatinine increase interval has been assimilated to the rest of the definitions of acute kidney injuries according to the KDIGO classification (AKI criterion),[16] changing from baseline creatinine increases between 48 and 72 h after the injection of contrast equal to or greater than 0.5–0.3 mg/dl. The reduction of the creatinine value of 0.5 mg/dl or more to 0.3 mg/dl or more is appreciated by nephrologists when unifying with other causes of AKI and because that is the interval from which there is considered to be kidney damage with clinical consequences.[16]

Routes of administration of contrast media

There is a significant change in the classification of the type of administration of intra-arterial iodinated contrast media: from the classic concept of intra-arterial injection (any injection of contrast media made through an artery), intra-arterial injection is now differentiated for first-pass and second-pass exposure. There are no changes in the concept of intravenous contrast administration.

An intra-arterial injection with first-pass renal exposure indicates that the contrast agent reaches the renal arteries in a relatively concentrated form, e.g. injection into the left heart cavities, thoracic or abdominal adrenal aorta or renal arteries.

An intra-arterial injection with second-pass renal exposure indicates that the contrast agent reaches the renal arteries after dilution in the pulmonary or peripheral circulation, e.g. injection into right heart cavities, pulmonary or carotid arteries, subclavian, coronary, mesenteric or infrarenal arteries.[13–15]

By way of criticism, it is worth mentioning that the ESUR guidelines 10.0 do not provide scientific evidence that justifies the differentiation of intra-arterial first- and second-pass renal exposure linked to the use of contrast and renal risk. It should also be noted that coronary angiography is included as an example of second-pass intra-arterial injection when precisely most of the evidence of renal risk and differences between contrasts are based on coronary angiography, taking into account that although coronary angiography can be considered a second-pass arterial injection, the ventriculography that is often associated with this exploration would be first-pass.[17,18]

Risk factors associated with the patient

The main risk factor according to the ESUR guidelines 10.0 is that the patient has acute or chronic impaired renal function. A patient being critical is also considered a risk factor.

On the other hand, the renal impairment threshold from which prophylaxis of PC-AKI will be carried out has been reduced in the majority of cases from a glomerular filtration rate (GFR) of less than *45–30 ml/min*.

In the case of intravenous or second-pass arterial injection, prophylaxis will only be performed in patients with a GFR of less than 30 ml/min/1.73 m².

In the case of first-pass intra-arterial injection, critically ill patients and/or patients with acute renal failure, the threshold will be a GFR of less than 45 ml/min/1.73 m².[13–15]

The ESUR guidelines 10.0 omit non-renal risk factors that were included in the ESUR 9.0 recommendations, such as diabetic nephropathy, hypotension, congestive heart failure, dehydration, sepsis, hypoxia, liver cirrhosis, administration of nephrotoxic drugs and kidney transplantation.[7]

According to the ESUR guidelines 10.0, the only drug that should be discontinued before injection of an iodinated contrast medium is metformin, but only in patients with a GFR less than 30 ml/min. Remember that metformin is not nephrotoxic, but can exceptionally produce lactic acidosis in patients with renal impairment.[19] Taking into account that metformin is generally contraindicated with a GFR <30 ml/min, we would withdraw it only in exceptional cases from the moment of the examination until 48 hours after the administration of the iodinated contrast medium. As a general rule we can conclude that the new ESUR guidelines 10.0 advise not to discontinue any medication.

In contrast, the KDIGO 2012 guidelines (*Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*) recommend that all people with a GFR < 60 ml/min (GFR categories 3–5) who undergo an imaging test that involves intravascular administration of iodinated contrast media undergo an elective investigation of possible associated risk factors for nephropathy. According to this guide, it is recommended to show risk factors such as age, hypotension, diabetes, dehydration, nephrotoxic agents, heart failure and anaemia.[16] It is true that KDIGO admits that although the risk of PC-AKI increases with a GFR <60 ml/min, PC-AKI is particularly high (7.8% in one study) when the GFR is less than 30 ml/min and that implementing preventive strategies for all patients with a GFR < 60 ml/min may not be practical. However, it considers that a gradual risk assessment, taking into account all risk factors, is more realistic.[16]

On the other hand, in its 2016 onconephrology educational programme, the American Society of Nephrology recognises that cancer patients require a special approach (due to multiple examinations, combination of nephrotoxic drugs, complex haemodynamic situations, etc.) to prevent PC-AKI, and establishes a series of preventive measures in patients with a GFR < 60 ml/min, including limiting the volume of contrast medium, using isoosmolar contrast, prehydrating with saline and interrupting concurrent nephrotoxic agents,[20] and this has recently been editorialised by the journal *Nephrology*.[21]

Risk factors associated with the contrast medium

- *Intra-arterial administration with first-pass renal exposure.*
- *Large doses of contrast media injected by first-pass arterial route.*
- *Hyperosmolar contrast medium.*
- *Multiple contrast medium injections injected in 48–72 h.*[14,15]

The guide advises that iodinated contrast medium injections should not be repeated within a short time and that the minimum possible dose of contrast medium adjusted to weight be injected. No differences are found between hypoosmolar and isoosmolar contrast injection.[22]

The recommended intervals between two tests performed with contrast media are specified in the ESUR guidelines 10.0.[14,15]

High osmolarity contrast media (2100–2400 mOsm/kg H_2O) have clearly demonstrated nephrotoxicity and are no longer used in radiological examinations. ''Low'' osmolarity media (577–823 mOsm/kg H_2O) are actually hyperosmolar because they have an osmolarity greater than that of plasma (290 mOsm/kg H_2O). The arrival of isoosmolar contrast medium (290 mOsm/kg H_2O) was presented in prospective randomised studies as very beneficial in the prevention of kidney damage after generally coronary intra-arterial injection, with many meta-analyses favouring iodixanol (isoosmolar) over other low osmolarity contrasts as a group and in particular compared to iohexol, which accounts for the largest number of studies.[23–26] The beneficial data on isoosmolar contrast media were not found strongly in intravenous administration, perhaps due to the small number of studies and methodological problems, such as selection biases, which eliminate administration in high-risk patients, or limitations in the standardisation of sampling, given that the majority of intravenous studies did not standardise sampling during the post-contrast creatinine elevation period.[24] Currently, many nephrologic clinical guidelines advise using isoosmolar contrast in patients with risk factors for AKI.[16,21,27]

Prophylactic regimen for PC-AKI

The steps to carry out the prophylactic regimen according to the ESUR guidelines 10.0 are described below:

- *Consider an alternative imaging study that does not require the administration of an iodinated contrast medium.*
- *Preventive intravenous hydration protocols with saline and bicarbonate have similar efficacy.*
- *For administration of intravenous or intra-arterial contrast medium with second-pass renal exposure in patients with a GFR less than 30 ml/min/1.73 m², hydrate the patient with (a) intravenous sodium bicarbonate 1.4% (or 154 mEquiv./l in serum with 5% dextrose) at 3 ml/kg/h for 1 h before contrast medium administration or (b) intravenous saline solution 0.9% 1 ml/kg/h for 3–4 h before and 4–6 h after contrast medium administration.*
- *For the administration of intra-arterial contrast medium with first-pass renal exposure in patients with glomerular filtration rate of less than 45 ml/min/1.73 m² or in critical patients, hydrate the patient with (a) intravenous sodium bicarbonate 1.4% (or 154 mEquiv./l in serum with 5% dextrose) at 3 ml/kg/h for 1 h before the contrast medium, followed by 1 ml/kg/h for 4–6 h after administration or (b) intravenous saline solution 0.9% 1 ml/kg/h for 3–4 h before and 4–6 h after contrast medium administration.*
- *The physician responsible for patient care should individualise preventive hydration in patients with severe congestive heart failure (NYHA grade 3–4) or end-stage renal failure (GFR < 15 ml/min/1.73 m²).*
- *Oral hydration is not recommended as a lone preventive hydration measure.*
- *Determine GFR within 48–72 h after contrast medium administration. If the diagnosis is PC-AKI, clinically monitor the patient for at least 30 days and measure the GFR at regular intervals.*
- *No pharmacological prophylaxis (renal vasodilators, endogenous vasoactive mediator receptor antagonists or cytoprotective drugs) has been shown to offer consistent protection against post-contrast acute injury.*[14,15]

Regarding the type of hydration, the guide concludes that the effect of hydration with bicarbonate and with physiological serum is equivalent, but bicarbonate is preferred for short regimens (1 h before CT or second-pass arterial and 1 h–4/6 h for first-pass arterial or second-pass with GFR less than 15 ml/min), since the scientific evidence of these bicarbonate guidelines is more robust,[27] although as indicated by the ESUR guidelines 10.0[14] and recently demonstrated in the

PRESERVE trial,[28] the short regimens previously described with saline may be used if necessary.

On the other hand, there is not enough scientific evidence to equate the effectiveness of oral hydration with intravenous hydration. At the moment it is not recommended as the only prophylactic formula, although recent articles have already demonstrated its effectiveness.[10] In our hospital, when implementing the ESUR guidelines 10.0 and lowering the prophylactic hydration threshold from 45 to 30 ml/to prevent patients from going into the test with a fluid restriction of 4 or 6 h, which is considered a risk factor in itself due to its potential to cause dehydration, we recommend oral hydration to all patients (except those with restricted fluids) in the referral note, which consists of drinking 500 ml of water 2 h before the test and drinking 2000 ml of water over 24 h after the test.

In patients with a GFR less than 15 (stage 5 CKD) or severe heart failure (NYHA grade 3–4), liver failure, dialysis or any other pathology that causes the patient to have fluids restricted, the nephrologist, cardiologist or their specialist or GP will individually assess the appropriateness of examination with iodinated contrast and the type, volume and duration of prophylactic hydration.[14]

Final considerations for clinical practice

The new ESUR guidelines 10.0 have relaxed the assumptions under which the patient who is going to be tested with iodinated contrast should receive prophylaxis. These assumptions have been incorporated into the majority of radiological guidelines worldwide,[27,29] although there are some radiological and nephrological societies that disagree on this restriction of risk factors for prophylaxis against PC-AKI.[21,27] It is true that for ethical reasons, randomised prospective studies cannot be carried out to clear up the doubts that we have been explaining in this article, and it is also true that studies that have been conducted using the Propensity Match Score may have a margin of error.[30]

In the clinical community, and especially nephrology, these guidelines have been received with concern and warnings that this relaxation may lead to an increase in PC-AKI.[21,27]

We believe that these new guidelines can generally be safely implemented. However, in especially labile patients with risk factors associated with nephropathy and/or requiring repeated radiological tests with contrast media (e.g. cancer patients), additional measures can be taken such as prophylaxis with a GFR below 45 ml/min, withdrawal of nephrotoxic medications, longer prophylaxis or recommending the use of isoosmolar contrast.

Authorship

All authors have participated in the drafting of this manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Editorial

Post-contrast acute kidney injury in cancer patients☆

Lesión renal aguda poscontraste en pacientes con cáncer

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According to data of the Spanish Society of Medical Oncology,[1] cancer continues to be one of the main causes of morbidity world in continuous growth. Studies in Population indicate that the number of new cases is likely to increase by 70% in the upcoming decades, reaching approximately 24 million cases in 2035. Also in Spain, cancer is one of the main causes of morbidity, with 228,482 estimated cases for the year 2017 and it is predicted 315,413 cases for the year 2035.

In the evaluation of the cancer patient, the information obtained through radiological procedures using contrast media (CM) is of great importance for the diagnosis and evolution of the disease, and the CMs are increasingly used to obtain better images in a broad spectrum of techniques such as computed tomography (CT) and magnetic resonance imaging.

Cancer and kidney

The relationships between cancer er and kidney are being analyzed with more precision. Presently there multiple etiologies that are well known : acute or chronic renal failure (ARF, CKD), hydroelectrolytic disorders, glomerular nephropathies, toxic effects of different chemotherapies, etc. Of all these renal complications, post-contrast acute renal injury (AKI) (PC-AKI) has been widely discussed, especially strategies for prevention. In the case of the cancer patient, the possibility of AKI is accentuated for several reasons, underlining: the coincidence with other nephrotoxic factors, situations of inadequate renal perfusion, the frequent administration of iodinated contrast (CT

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and PET-CT with contrast) which is essential for the correct assessment of the neoplastic disease and in many cases the existence of previous renal insufficiency (glomerular filtration rate (GFR < 60 ml/min/1,73 m^2). There are recent studies that consider that PC-AKI is a transitory state with elevations in serum creatinine values with no clinical expression.[2] There are, however, studies that have shown that short and long-term mortality rates are significantly higher in patients with PC-AKI as compared to patients without PC-AKI.[3] In addition, the history of PC-AKI may be associated with the development of chronic kidney disease (CKD) and long term progression to end-stage renal disease.[4,5]

Risk factors for post-contrast acute kidney injury

One of the several modifications of the recommendations recently published in the new guides of the European Society of Urogenital Radiology (ESUR 10),[6,7] is the change of the denomination of AKF induced by iodinated contrast is changed to AKI associated to contrasts (AKI-PC); since in most cases, the kidney injury is coincidental and not necessarily caused by the contrast.

One of the most important changes in these new recommendations has to do with the risk factors related to the patient and specifically with cancer patients. Renal insufficiency continues to be considered as the most important risk factor for AKI-PC. However, other risk factors previously included have been excluded. According to the authors of the latest ESUR version 10, many meta-analyzes and systematic reviews of uncontrolled studies have identified a large number of possible clinical risk factors for AKI in general, such as advanced age, female gender, low body mass index, classic cardiovascular and metabolic risk factors, malignancy, inflammation, bleeding, anemia and hyperuricemia.[6] However, an objection is that in uncontrolled studies the baseline clinical risk factors cannot be reliably differentiated from the specific effects of the contrast. And based on this, the authors consider only as risk factors, in addition to renal failure, dehydration and the critical state or multiorgan failure of the patient. Age, the presence of a single kidney and the history of transplantation (renal, pancreatic or hepatic) are no longer considered risk factors. Stage 3 or 4 heart failure (according to the NYHA classification) is not a risk factor in itself, but it is the fact that it prevents proper hydration of the patient due to the restriction of fluids involved. The last ESUR 10 recommendations excluded the cancer patient as a risk factor for AKI-PC, however for the reasons explain below we do not share this decision.

Why does the cancer patient is at high risk for acute renal injury after contrast?

The cancer patient has a higher risk of acute kidney injury

There are many studies showing an increased risk of AKI for any cause in the cancer patient. In a Danish study that includes 37,267 cancer patients, the risk of AKI (defined as > 50% increase in serum creatinine values) was 17.5% after one year of diagnosis and 27% at 5 years.[8] In hospitalized patients without cancer, the incidence of AKI was 5%, while it reached 12% in cancer patients.[9]

In a cancer reference center with 3558 patients, the possibility (OR) to develop AKI was significantly greater in the presence of a number of risk factors, highlighting the use of CM: diabetes (OR 1.89; 95%, confidence interval [CI] 1.51–2.36), chemotherapy (OR 1.61; 95% CI, 1.26–2.05), intravenous contrast (OR 4.55; 95% CI, 3.51–5.89), hyponatremia (OR 1.97; 95% CI, 1.57–2.47) and antibiotics (OR 1.52; 95% CI, 1.15–2.02).[9] And this higher risk of developing an ARI (including cancer patients) has its consequences: an increase in hospital stay, mortality and costs.[10]

Age and renal failure

In the cancer patient, the increased age is associated frequent renal alterations. The average age of patients at the time of cancer diagnosis is 65 years. Of the 47% of cancer survivors, almost half are 70 years of age or older and only 5% are under 40 years.[11] The aging of the population increases the number of patients whose cancer is complicated by other chronic diseases. In the EPIRCE study, by the Spanish Society of Nephrology, on the general Spanish population,[12] 22% of adult patients over 65 years of age had a GFR < 60 ml / min / 1.73 m^2.

The data reporting renal failure (GFR < 60 ml / min / 1.73 m^2) in cancer patients at all ages are variable: from 18% in the BIRMA[13] study to 22% in the US. UU.[14] or 25% in Japan.[15] In a study conducted by us in hospitalized oncology patients in Spain, 18. 2% had GFR < 60 ml / min / 1.73 m^2).[16]

Therefore, a second reason for AKI-PC is the high percentage of kidney failure in cancer patients especially those in which the cancer is more common with age >65 years.

Nephrotoxic treatments

A 50% of anticancer drugs are predominantly excreted in the urine and 80% of patients receive potentially nephrotoxic drugs and / or for whom the dose should be adjusted.[13] The presence of pre-existing renal failure may limit the use of otherwise active regimes that may be curative. This combination of cancer, kidney disease and mortality has led to the recognition that Nephrology and Oncology are closely linked and the birth of the subspecialty, Onco-Nephrology.[17]

Many cancers affect kidney function. Some directly, such as myeloma, others by infiltration of the renal parenchyma in leukemia and lymphomas, cast nephropathy, obstruction or secondary glomerulopathies. Others indirectly, through volume depletion (vomiting, diarrhea, ascites, etc.), sepsis, heart failure or metabolic disorders such as hypercalcemia. It is important to consider, especially in the cancer patient, that the combined effect with other potentially nephrotoxic drugs, such as iodinated contrast, increases the risk of kidney damage.[18] Sendur et al. found that in patients with exposure to CM a week before the administration of cisplatin, the risk of AKI-PC was significantly higher than in patients without such exposure.[19]

Frequency of studies with contrast media

The recommendations for staging and monitoring cancer treatments require evaluations that includes frequent imaging tests with iodinated contrast. In most tumors, thoracoabdominal CT with contrast is recommended every 3 or 6 months for the first 2 or 3 years and even more frequently if the patient is included in a clinical trial, and annually until the 5th or even the first 10 years.[20,21]

It is not clear if the repetition of radiological studies with administration of iodinated contrasts, as in the case of some cancer patients, increases the risk of AKI-PC. The studies are often observational retrospective, with many differences among patients in relation to hydration, dose and type of contrast, route of administration, comorbidities, association of nephrotoxic drugs, etc. Even studies using Propensity Machted Score (PMS) adjusting certain variables are not exempt from bias by indication. However, Hsieh et al.[22] studied with PMS 7100 patients with non-advanced CKD receiving contrast CT and using PMS they adjusted another population of 7100 patients undergoing by CT but without contrast. They found a much higher risk of developing ESRD in the 2 groups exposed to >1 and <2 contrast per year and a mean of ≥2 exposures per year (adjusted HR = 8.13, 95%, CI, 5.57–11.87 and adjusted HR = 12.08, CI 95%, 7,39–19.75, respectively) as compared with patients who underwent CT without using contrast medium. It seems that what represents a clear risk of kidney damage is the repeated exposure to contrast at 36−72 h or performing urgent radiological studies. Similarly, in the series by Chan et al. in cancer patients, the absolute risk after contrast CT increases from 0.3 to 2.3%, depending on the type of cancer.[23]

Loss of renal functional reserve or hidden renal damage

The renal functional reserve (RFR) represents the ability ofthe kidney to increase the GFR in response to certain stimuli that can be physiological (high protein intake, amino acid infusion) or pathologic (first stage of diabetes). The difference between the the maximum FGR and the basal GFR represents the RFR. There may be a damaged kidney in which the loss of FG is compensated by intact nephrons that function as the RFR, an d the increase in serum creatinine does not occur. The RFR may be is lost after the repetition of renal injuries (decompensation of failure heart, ischemia / reperfusion, repeated use of iodinated contrasts or nephrotoxic drugs). And this may happen especially in cancer patients. Therefore, in the absence of an elevation of the serum creatinine, AKI may not be ruled and the possibility subclinical kidney damage after repeated injuries not can be ruled out.[24] Some studies that must be confirmed point to the value of serum NGAL and FGF23 determinations in the early diagnosis of AKI-PC.[25]

Prevention of post-acute acute renal injury in the cancer patient

For all the above reasons, preventive specific measures must be implemented in the cancer patient. In the series by Chan Ng et al.[23] a patient hospitalized with cancer receiving contrast CT has a 2.4% baseline risk of developing AKI-PC. This risk increases progressively in patients with CKD stage 1 (4.9%), 2 (7.0%), 3 (9.6%) and 4–5 (10.5%), so in the cancer patient it is very important to consider the degree of CKD.

It is advisable as a preventive measure (in addition to adjustment of the contrast dose to the GFR) the correct hydration, without differences between saline and bicarbonate. There are also no differences between oral N-acetylcysteine and placebo.[26] The use of oral (rather than intravenous) hydration is not recommended in patients at risk of AKI, as is the case in cancer patients, with some exceptions.[27] Recently, it has been shown that prolonged fasting for liquids and solids is in itself a risk factor for developing AKI-PC due to the dehydration that may cause to the patient. Currently, it is recommended to advise the patient correct and profuse self-hydration, and in many hospitals, fasting of solids is not performed, increasing the well-being of the cancer patient.[28]

Recommendations of different guides on the type of contrast medium for prevention of acute post-contrast renal injury

ESUR 10 does not refer to differences between low osmolarity contrast injection (577–823 mOsm / kg H_2O) and isoosmolar (290 mOsm / kg H_2O).[6] However, the isoosmolar iodixanol CM induces less cytotoxic effects in cultured tubular cells and the production oxididated radicals is less than lowosmolarity iohexol and iopamidol.[29] In addition, in high-risk patients, the iodixanol isoosmolar dimer is associated with less nephrotoxic effects than the lowosmolarity.[30]

The incidence of AKI-PC, dialysis or mortality in patients at high risk adjusted for PMS was similar in CT with isoosmolar (iodixanol) than in patients who did not receive contrast. This may not be applied to low osmolarity contrasts in high-risk patients.[31]

The use of isoosmolar CM is contemplated in different guidelines on the prevention of AKI-PC:

- ACCF / AHA / ACP / AATS / PCNA / SCAI / STS: state: to avoid the worsening of the underlying disease "use a renal protection strategy that includes the use of isoosmolar MC during angiography".[32]
- American Society of Nephrology: Geriatric nephrology curriculum 2009: older patients are more frequently subjected to invasive procedures, nephrotoxic medications and CM that increase the risk of AKI. Renal protection strategies include, among others, intravenous hydration and isosmolar CMs.[33]
- KDIGOGuides 2012[27] : recommend that all persons with GFR < 60 ml / min / 1.73 m^2 (GFR stages G3a-G5) undergo elective evaluation involving intravascular administration of radioiodinated media according to the K DIGO Clinical Practice Guide for AKI, which includes, among others:
- Identify risk factors such as diabetes, dehydration, nephrotoxic agents, heart failure, cancer patients, etc.
- Avoid high osmolarity agents (1B). Isoosmolar agents, in comparison with low osmolarity agents, are associated with lower rates of AKI in some, but not in all studies. Wherever possible, the isoosmolar agents should be used in individ-

uals with CKD with high risk of AKI (GFR <30 ml / min / 1.73 m^2).
- The American Society of Nephrology in its 2016 educational program in Onco-Nephrology, recognizes that the cancer patient needs a special approach (by multiple tests, association of nephrotoxic drugs, complex hemodynamic situations, etc.) to prevent AKI- PC they establishes a set of preventive measures in patients with GFR < 60 ml / min, including limiting the volume of contrast, using iso — osmolar contrast, prior hydration with normal saline and discontinue concurrent nephrotoxic agents.[34]
- Guidelines for Medicines Optimization in Patients with Acute Kidney Injury July 2016 NHS England with UK Renal registry: contrast induced nephropathy (CIN) is increased with high or low osmolarity contrast as compared with with isoosmolar contrast.[35]
- Low contrast volumes can reduce AKI -PC rates and it is recommended to use the lowest possible dose of contrast medium to reduce the risk.[36]

In conclusion

We believe that the oncological patients should be included as a high-risk group in view of the possibility of AKI-PC. Taking into account that a eGFR value of < 30 ml / min / 1.73 m^2 is too limited and inaccurate, since 20–30% of the estimated FG have an error from the measured eGFR value,[37] our position for cancer patients with FG < 45 ml / min / 1.73 m^2 (pending prospective randomized studies)would be:

- Adjustment of the dose of contrast to the GFR.
- Prophylaxis with intravenous hydration.
- Suspend nephrotoxic medication and adapt the examination according to cancer treatment (cisplatin).
- Use isoosmolar contrast if:
- eGFR < 30 ml / min / 1.73 m^2 (or creatinine > 2 mg / dl).
- it is intraarterial administration.

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Research Article

The Safety of Computed Tomography Angiography in Patients Suffering from Pre-Dyalitic Renal Failure

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- Computed tomography
- Contrast induced nephropaty
- End-stage renal disease
- Transplantation
- Preemptive

Abstract

Background: The aim of this study is to evaluate the prevalence of Contrast Induced Nephropathy (CIN) and the need for dialysis in pre-emptive living donor kidney recipients who undergo a Computed Tomography Angiography (CTA) after CIN prophylaxis to evaluate safety of iodinated contrast administration in these patients.

Material and methods: Thirty-eight patients with end-stage renal disease (ESRD), chronic kidney disease (CKD) stage 4 and 5, awaiting a pre-emptive living donor transplant underwent a CTA as part of the pre-transplant evaluation. All patients received a CIN prophylactic regimen using sodium bicarbonate 1/6M at 3 mL/kg/h starting 1hour before the CTA and 1 mL/kg/h six hours following the procedure and three doses of N-Acetylcysteine (1200 mg/12h) starting 12 hours before CTA. The variables analyzed were plasma creatinine levels (15 days before and immediately before CTA and 48-72 hours after and 14 days after CTA) as well as the need for dialysis during the follow-up.

Results: Mean creatinine levels 14 days before and immediately before CTA, within 72 hours after and 14 days after CTA were 4.45 (R 1.76-7.30), 4.56 (R 2.00-7.0), 4.59 (R 2.09-6.98) and 4.73 (R 1.65-7.9) mg/dl respectively. Only four (10.5%) patients showed CIN, which was reversible in 3 cases. Further worsening of renal function was detected in only one patient (2.6%). None of the four patients required dialysis before transplantation.

Conclusion: In patients with CKD stages 4 and 5, the use of intravenous contrast media combined with CIN prophylaxis is safe not leading to an early initiation of dialysis.

ABBREVIATIONS

CTA: Computed Tomography Angiography; CIN: Contrast Induced Nephropathy; NAC: N-Acetyl Cysteine; ESRD: End-Stage Renal Disease; GFR: Glomerular Filtration Rate

INTRODUCTION

Pre-transplantation screening evaluation is compulsory to stratify the risks and leads of kidney transplantation. Computed tomography angiography (CTA) is used for pre-transplantation vascular mapping, in patients older than 40 years or with cardiovascular risk factors, mainly to assess atherosclerosis in the arterial iliac and splenic system. In patients with long time in dialysis, contrast- enhanced CT may also be used to rule out the presence of renal cell carcinoma associated with acquired renal cystic disease [1-7]. Concurrent abdominal diseases and venous problems abnormalities can also be assessed by CTA [8].

CIN is defined as an increase in serum creatinine of 0.5mg/dl or more within 72 hours after contrast administration in absence of other causative factors [9]. In pre-dialysis patients awaiting for kidney transplantation, performing a CTA examination could be of concern as it may result in acute renal failure that could lead to an early initiation of dialysis. Although CIN incidence seems to be lower than previously described, it is well known that patients with a glomerular filtration rate (GFR) lower than 30 ml/min

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are at a higher risk of increased creatinine levels, transient or permanent, or even of early initiation of dialysis [10,11].

The aim of this study is to evaluate the prevalence of CIN and the need for dialysis in pre-dialysis patients who underwent a CTA with intravenous iodinated contrast for pre-transplant evaluation with CIN prophylaxis to demonstrate the safety of administration of iodinate contrast in these patients. As far as we know, there is only one study that deals with this topic [12].

MATERIAL AND METHODS

This is a prospective single-center study that was approved by the Ethics Committee of our hospital. Thirty-eight patients with chronic kidney disease (CKD) stage 4 and 5 who were candidates for pre-emptive living donor kidney transplantation for whom CTA was indicated were included between January 2011 and March 2013. All patients provided informed consent. All patients had a Modification of diet in renal disease estimated GFR lower than 30 ml/min. Exclusion criteria included patients [1] awaiting to kidney-pancreas transplantation [2] in whom prophylactic hydration is contraindicated (presence of uremic symptoms, symptoms suggestive of cardiac insufficiency class III-IV based on the New York Heart Association classification), and [3] with a history of allergy to iodinated contrast.

For CIN prophylaxis patients were instructed to take three doses of N-acetylcysteine (1200 mg every 12 hours starting 12 hours before the CT-scan). On the day of the procedure, the patients were infused with 3mL/kg/h of sodium bicarbonate 1/6M 1 hour before the CT examination and 1mL/kg/h six hours following the procedure. On average, 671 cc of saline were administered (2/3 after the examination). Patients were discharged six hours after the CT examination.

The CTA protocol involved scanning of the abdomen and pelvis using a Siemens Sensation 64 or Siemens Flash (Siemens, Erlargen, Germany) as part of the pre-transplantation evaluation. The study protocol involved an unenhanced phase CT (craniocaudal, from diaphragm to pubic symphysis, 30x1.2 mm) and two enhanced phases obtained after the injection of 100ml of a monomeric hypo-osmolar non-ionic contrast (iopromide Ultravist® 300mg/ml) + 40ml of saline at 4ml/s. Timing for arterial phase CTA (64x0.6 mm) was determined with CARE bolus, ROI at the abdominal aorta, a threshold of 120 UH; and six second delay. Nephrographic phase images were obtained 90 seconds following the administration of IV contrast material (30x1.2 mm). Axial reconstructions were obtained at the end of each phase. Multiplanar and volume rendering reconstructions of the aortoiliac system and branches were obtained in the post-processing workstation in all cases.

Analysis: All patients were closely followed before and after the CTA and until the time of transplantation. Blood samples were taken 14 days and immediately before CTA as within 48-72 hours and 14 days after the CTA. When no significant deterioration of the renal function was observed, patients continued the usual follow-up for renal insufficiency. In case of renal function decline, patients were appropriately managed.

Variables analyzed: The primary endpoint evaluated was the need for renal replacement treatment after CTA, before renal transplant. Secondary endpoints were the appearance of CIN (increase of 0.5mg/dl in plasma creatinine within 72h after administration of contrast) and reversible or permanent increase of creatinine levels in CIN patients.

Statistical analysis

Summary statistics were described as frequencies and proportions for categorical variables. Chi-square tests were used to determine the correlation between qualitative variables. Median values were compared using t-tests (95% confidence intervals). p-values <0.05 were considered statistically significant. Data documentation and analysis were performed using SPSS v.15 (IBM Corp., Somers, NY, USA).

RESULTS

Thirty-eight patients were included in the study, with a mean follow-up of 5.23 months (range 0.23-36.83). The ratio male: female was 28:9, with a mean age of 52.7 years (range 32.1-77.25). Demographic data are shown in (Table 1). Of all these patients, 29 (78,4%) underwent kidney transplantation, with a mean time between the CTA imaging and the transplantation of 106 days (range 7-1105).

The average creatinine level 14 days before, immediately before, within 72 hours and 14 days after the CTA procedure were 4.45 (range 1.76-7.30), 4.56 (range 2.00-7.0), 4.59 (range 2.09-6.98) and 4.73 (range 1.65-7.9) mg/dl respectively . Four patients (10.5%) developed CIN, with a significant decrease in creatinine levels 15 days post-procedure in three of them, the fourth patient (2.63%) showed progressive worsening of creatinine levels (Table 2). Table 3 shows no significant differences in demographics between CIN and no-CIN patients.

None of the 29 patients that underwent kidney transplantation needed dialysis before surgery. Of the 9 patients who did not undergo kidney transplantation, 7 started dialysis 161 (range 33-346) days in average after the scan, one died due to a lymphoma and the other was submitted to a liver transplantation with improvement of the kidney function. None of these 9 patients developed CIN or early dialysis after CTA.

Despite the fact that there was a significant increase in

Table 1: Baseline characteristics.

Variable	[1]
Age (y), mean ± SD	54.10 ± 11.64
Male, n (%)	28 (73.68%)
DM type II, n (%)	2 (5.26%)
Hypertension, n (%)	32 (84.21%)
ACE-inhibitor or ARB use, n (%)	19 (50%)
Diuretic use, n (%)	10 (26.31%)
Serum creatinine (mg/dL) mean ± SD	4.45 ± 1.26
eGFR (MDRD) mean ± SD	16.10 ± 7.07
Serum bicarbonate (mg/dL) mean ± SD	21.60 ± 3.39

CIN: Contrast-Induced Nephropathy; SD: Standard Deviation; ACE-inhibitor : Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker

Sebastià et al. (2016)
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Table 2: Changes in creatinine levels in patients that developed CIN. Case 3 had a permanent worsening of the renal function. None of the patients needed dialysis before transplantation.

Creatinine (mg/dl)	15 days pre-CTA	day CTA pre-CTA	72h post-CTA	15 days post-CTA
Case 1	5.1	5.9	6.5	6
Case 2	4.4	4.9	5.5	5.2
Case 3	5.93	5.7	6.2	6.7
Case 4	3.47	3.9	5.04	4.2

Table 3: Comparison of baseline characteristics between patients who developed NIC and patient who did not.

Variable	CIN n = 4	Non-CIN n = 34
Age (y), mean ± SD	47 ± 10.39	54.96 ± 11.63
Male, n (%)	4 (100%)	24 (71%)
DM type II, n (%)	0 (0%)	2 (6%)
Hypertension, n (%)	4 (100%)	28 (82%)
ACE-inhibitor or ARB use, n (%)	2 (50%)	17 (50%)
Diuretic use, n (%)	1 (25%)	9 (26%)
Serum creatinine (mg/dL) mean ± SD	4.84 ± 0.87	4.40 ± 1.32
eGFR (MDRD) mean ± SD	14.5 ± 0.87	16.30 ± 7.54
Serum bicarbonate (mg/dL) mean ± SD	22 ± 3.68	21.55 ± 3.46

CIN: Contrast-Induced Nephropathy; SD: Standard Deviation; ACE-inhibitor: Angiotensin-Converting Enzyme inhibitor; ARB: Angiotensin Receptor Blocker

average creatinine between the levels obtained immediately before the CTA procedure and 14 days post-procedure in the patients of our series, the increases in creatinine levels obtained 14 days pre-procedure and immediately before CTA and between creatinine levels immediately before CTA and 14 days pots procedure were similar (0,13 vs 0,30, respectively p>0,29) (Figure 1). The increase in creatinine observed in the only patient with CIN, whose renal function progressively worsened, could be due to the progression of the ESRD.

DISCUSSION

Enhanced CT is usually avoided in pre-dialysis patients with CKD stages 4 and 5, waiting for transplantation as it is considered to worsen the renal function, eventually leading to earlier dialysis initiation related to iodinated CIN [9]. The incidence of CIN following IV iodinated contrast administration has been recently reevaluated and its existence questioned even in end stage renal disease (ESRD) patients [11], but most of the literature states that chronic renal failure is an independent risk factor [10].

Several strategies have been used for the prophylactic prevention of CIN. Latest guidelines suggest that IV hydration with saline or bicarbonate is the most effective measure of prophylaxis [12]. The use of NAC is controversial, in fact, it has been excluded from the most recent guidelines [13].

The increasing number of living donor transplantations allows us to plan the surgery and to know the exact day of transplantation. In patients who receive transplants from living donors a CTA can be performed weeks before the transplantation date for vascular mapping and repercussions of a potential worsening of the renal function will not relevant given the proximity of transplant surgery. The evaluation of patients receiving transplants from living donors allows us to determine the actual incidence of NIC in CKD stage 4 and 5 patients after CIN prophylaxis.

We only found four patients (10.5%) with significant increase in creatinine levels consistent with CIN. This increase was reversible in three of the four patients. Newhouse et al. have reported that spontaneous oscillations of creatinine occur in the general population, with a similar incidence of CIN to that found

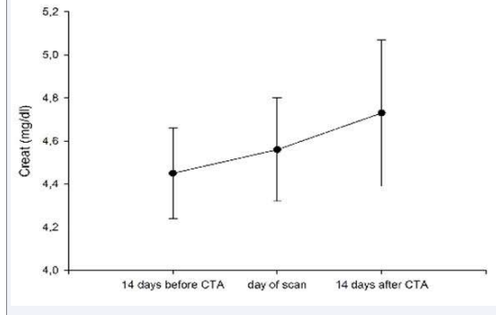

Figure 1 Changes in creatinine levels 15 days before CTA, immediately before CTA and 15 days after CTA. No significant differences were found in creatinine increase from 15 days pre-CTA to immediately before CTA and from immediately before CTA and 15 days after CTA. The permanent worsening in the patient that presented CIN can be not related to contrast administration but to the progression of ESRD.

in patients with chronic kidney disease [14]. Newhouse and other authors also found that fluctuations in creatinine are greater in CKD stage 4 and 5. In our series the increase of creatinine between 14 days pre-CTA and the moment previous to the procedure was not statistically significant compared to the increase between two days post-CTA and 14 days post-procedure. This casts doubt on whether the increase in creatinine is not a result of the natural course of the disease if no contrast would have been administered. It is worth noting that the two patients that required dialysis before transplantation did not have CIN and that none of the four patients with CIN needed dialysis before surgery.

To our knowledge there is only one study that deals with prophylaxis of CIN in pre-dialysis living donor recipients undergoing CTA [12]. In this retrospective study, 43 patients in pre-dialysis were evaluated oral hydration was administered before and after CTA. Four out of the 42 patients (9%) showed an increase in creatinine levels greater than 0.5mg/mL (CIN definition), but none of them required dialysis. These results are similar to the results presented here. In this study by Smith et al. the theoretical clinical management of 22.9% of patients was modified because of the CTA findings. In 15.8% of patients the site of anastomosis was influenced by CTA findings and in 3.4% of patients CTA demonstrated renal cell carcinoma.

There are two other interesting publications about the effect of intraarterial contrast administration after coronary angiography (CA) in patients waiting for pre-emptive transplantation: One is a retrospective study in which 62 patients with CKD stage 4 and 5 underwent CA with a CIN prophylaxis regimen involving NAC and intravenous saline hydration. In this study all of the cases of CIN (22%) showed only a transient decline in renal function during the first week post-CA that was entirely reversible, suggesting that intraarterial iodinated contrast administration did not accelerate the decline in renal function in patients with ESRD [16]. In another series the need for dialysis in 23 patients waiting for pre-emptive kidney transplant who underwent CA with oral hydration prophylaxis was compared with a control group of 23 patients who did not undergo CA. No differences in the need for dialysis were found between the two groups [17].

The results of the present study are similar to those of Smith et al [12]: none of the patients evolved into dialytic renal failure, differently to Smith et al who utilizes no prophylaxis rather than hydration, we utilized a protocol comprising of N-acetyl cysteine and sodium bicarbonate in order to prevent worsening of renal function. The similar results seems to say that no matter which hydration protocol is utilized who present with pre-dialytic endstage renal failure tolerate performance of CT-Angiography without evolving into dialytic endstage renal failure. It seem confirmatory that hydration is the key.

One limitation of this study is patients waiting for kidney-pancreas transplantation have not been included, therefore the conclusions can no be extended to patients waiting for kidney-pancreas transplantation. Further works including these patients are needed to know CIN incidence after intravenous contrast injection in this specific group.

Another limitation of this paper is the small number of patients and the absence of a control group. However, comparison of our results with those control groups (changes in creatinine levels in patients with CKD stage 4 and 5 after unenhanced CT) published in the literature has demonstrated similar results than ours [15].

CONCLUSION

Our conclusion is that CTA is a safe procedure when performed with CIN prophylaxis in CKD stage 4 and 5 with low contrast induced nephropathy rate and not inducing to an early initiation of dialysis. In our series only four (10.5%) patients showed CIN, which was reversible in 3 cases. Further worsening of renal function was detected in only one patient (2.6%). CTA can be included safely in the clinical guidelines for the imaging examination of pre-emptive living donor kidney recipients.

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9.2. Comunicacions i pòsters a congressos nacionals i internacionals

34 CONGRESO NACIONAL DE LA SOCIEDAD ESPAÑOLA DE RADIOLOGIA MÉDICA (SERAM). EDICIÓN VIRTUAL 19/26 MAYO 2021

Estudio randomizado comparando la hidratación oral versus hidratación endovenosa como profilaxis de la lesión renal aguda post-contraste en pacientes con insuficiencia renal crónica grado III.

A.Páez-Carpio, C. Sebastià, G. Serra, E,. Guillen, E. Poch, Carlos Nicolau.

VIII CONGRÉS NACIONAL DE RADIÒLEGS DE CATALUNYA. BARCELONA 29-31 DE MAIG DEL 2019.

Resultats del nostre protocol de profilaxi de la lesió renal aguda postcontrast i implementació de les guies ESUR 10.0 al nostre centre.Sebastià, R. Crespo, S. Falip, F. Zarco, L. Buñesch, C. Nicolau.

34 CONGRESO NACIONAL DE LA SOCIEDAD ESPAÑOLA DE RADIOLOGIA MÉDICA (SERAM). PAMPLONA 24-27 DE MAYO DEL 2018.

Prevalencia de la nefropatía inducida por contraste (NIC) realizando hidratación profiláctica en nuestro centro. Revisión de los últimos 4 años.

C. Sebastià, R. Crespo, S. Falip, F. Zarco, L. Buñesch, C. Nicolau

EUROPEAN CONGRES OF THE EUROPEAN SOCIETY OF RADIOLOGY. VIENA 2-6 MARCH 2016

To create a circuit for preliminary nursing visits schedule in patients with renal failure, when an imaging test with iodine-based contrast media is requested, to reduce contrast-induced nephropathy (CIN).

S. Falip, R. Crespo, C. Sebastià, L. Oleaga.

9.3. PREMIS

1. MAGNA CUM LAUDE A LA COMUNICACIÓ PRESENTADA AL 34 CONGRESO NACIONAL DE LA SOCIEDAD ESPAÑOLA DE RADIOLOGIA MÉDICA (SERAM). EDICIÓN VIRTUAL 19/26 MAYO 2021

Estudio randomizado comparando la hidratación oral versus hidratación endovenosa como profilaxis de la lesión renal aguda post-contraste en pacientes con insuficiencia renal crónica grado III.

A.Páez-Carpio, C. Sebastià, G. Serra, E. Guillen, E. Poch, Carlos Nicolau.

SERAM Sociedad Española de Radiología Médica

35 Congreso Nacional Edición Virtual 19/26 MAYO 2021 17/18 MAYO 2021 CURSO PREGONGRESO Simposio SERAM-RSNA

La Sociedad Española de Radiología Médica

Concede a:

Alfredo Páez Carpio, Carmen Sebastià, Gina Serra, Elena Guillén, Esteban Poch, Carlos Nicolau.

MAGNA CUM LAUDE

Por su **comunicación electrónica** presentada en el 35 Congreso Nacional SERAM:

OR-055. Estudio randomizado comparando la hidratación oral versus hidratación endovenosa como profilaxis de la lesión renal aguda poscontraste en pacientes con insuficiencia renal crónica grado III.

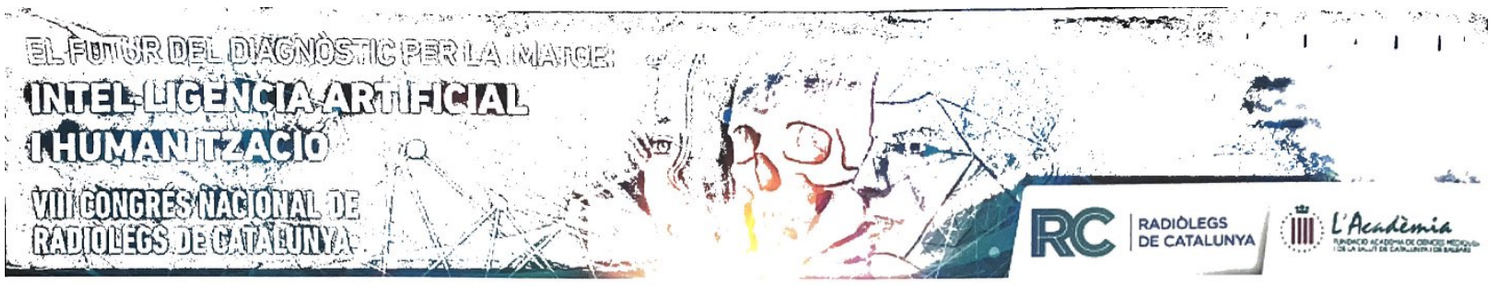
Madrid, 26 de mayo de 2021

Dr. Pablo Valdés Solís
Presidente Saliente SERAM
Presidente Comité Organizador

Dr. José María Artigas Martín
Presidente Comité Científico

2. ACCESIT AL MILLOR TREBALL CIENTÍFIC PRESENTAT AL VIII CONGRÉS NACIONAL DE RADIÒLEGS DE CATALUNYA. BARCELONA 29-31 DE MAIG DEL 2019.

Resultats del nostre protocol de profilaxi de la lesió renal aguda postcontrast i implementació de les guies ESUR 10.0 al nostre centre.Sebastià, R. Crespo, S. Falip, F. Zarco, L. Buñesch, C. Nicolau.



Per la present es concedeix el accèssit al millor treball científic a

MARIA DEL CARMEN SEBASTIA CERQUEDA

com primer autor de la comunicació titulada:

RESULTATS DEL NOSTRE PROTOCOL DE PROFILAXI DE LA LESIÓ RENAL AGUDA POSTCONTRAST I IMPLEMENTACIÓ DE LES GUIES ESUR 10.0 AL NOSTRE CENTRE

dels autors:

Carmen Sebastià Cerqueda; Raquel Crespo; Silvia Falip; Federico Zarco; Laura Buñesch; Carlos Nicolau

presentada durant el VIII Congrés Nacional de Radiòlegs de Catalunya celebrat a Barcelona del 29 al 31 de maig de 2019.

Dr. Salvador Pedraza
President del Congrés

Dr. Josep Munuera
President del Comitè Científic