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Što doista znamo o kontrastom induciranoj nefropatiji?

What do we really know about contrast-induced nephropathy?

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SAŽETAK: Porast broja dijagnostičkih i terapijskih postupaka s korištenjem kontrastnih sredstava povećava mogućnost razvoja kontrastom inducirane nefropatije (KIN). Zamjećeno je da se KIN razvija gotovo isključivo kod invazivnih kardiovaskularnih pretraga i zahvata, dok se tijekom CT-angiografskih pretraga razvija vrlo rijetko. Navedeni su rizični čimbenici za razvoj KIN, iznesene preporuke za praćenje renalne funkcije te navedeni mogući periproceduralni načini prevencije. Uz najčešće korištene ione joda kao radiokontrasta i uporaba gadolinija može u pacijenata s kroničnim bubrežnim zatajenjem izazvati nefrogenu sistemsku sklerozu koju ne možemo prevenirati niti adekvatno liječiti, pa je i uz pretrage magnetskom rezonancom s primjenom kontrasta kod nefroloških bolesnika potrebno pomno procijeniti rizik u odnosu na potencijalnu korist pretrage.

KLJUČNE RIJEČI: radiokontrastna sredstva, kontrastom inducirana nefropatija, kardiovaskularna dijagnostika.

SUMMARY: The increase in the number of diagnostic and therapeutic procedures by using contrast agents increases the possibility of developing of contrast-induced nephropathy (CIN). It has been noticed that CIN develops almost exclusively in invasive cardiovascular tests and procedures, while it develops very rarely during the CT-angiography. The risk factors for the development of CIN have been mentioned, recommendations for monitoring of renal function have been put forward and potential perioperative prevention methods have been mentioned. With most commonly used iodine ions as radiocontrast agents and the use of gadolinium, we can cause nephrogenic systemic sclerosis in patients with chronic renal failure, which sclerosis cannot be prevented or appropriately treated, and in addition to magnetic resonance imaging test with the use of contrast agents we should carefully evaluate the risks in relation to potential benefit of the test in nephrologic patients.

KEYWORDS: radiocontrast agents, contrast-induced nephropathy, cardiovascular diagnostics.

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Zadnje desetljeće provođenje pretraga s primjenom radiokontrasta u CT dijagnostici je poraslo za gotovo 800%, a kardiološke kateterizacije za oko 400%. Za orijentaciju o kojem redu vrijednosti se radi, navodi se podatak od pred deset godina kada je ta brojka iznosila osamdesetak milijuna doza radiokontrasta godišnje. Za pretpostaviti je da će nedvojbeno porasti i rizik nastanka bubrežnih oštećenja uslijed uporabe radiokontrasta ne samo zbog povećanog broja procedura, već i zbog sve više dobi pacijenata sa značajnim i brojnijim pridruženim bolestima od kojih je, svakako, najznačajnija šećerna bolest.

Nastanku kontrastom inducirane nefropatije (KIN) osobito su podložni bolesnici s već oštećenom bubrežnom funkcijom kojih je oko 10% u općoj populaciji. Uslijed neupitne povezanosti oštećenja bubrežne funkcije s povišenim rizikom nastanka kardiovaskularnih događaja[1], ti su bolesnici sve češće izloženi dijagnostičkim procedurama s radiokontrastom. Tome u prilog govori podatak kako je kod bolesnika s kroničnom bubrežnom bolesti koji još nisu započeli liječenje dijalizom registrirano 16% sa stabilnom, 5% s nestabilnom

During the last decade, conducting tests with the use of radiocontrast agents in CT diagnostics has increased by almost 800%, while the cardiac catheterization has increased by about 400%. For guidance as to which value is concerned, there is data that were actual some ten years ago when this figure was around eighty million doses of radiocontrast agent a year. We can assume that the risk of occurrence of kidney impairment will undoubtedly increase as a result of using radiocontrast agent not only because of an increased number of procedures, but also because of higher age of patients with significant and numerous associated diseases, of which diabetes is, of course, the most significant disease.

Patients with already impaired renal function, of whom there is 10% in the general population, are particularly vulnerable to contrast-induced nephropathy (CIN). Due to the undeniable connection between renal function impairment with an increased risk of cardiovascular events[1], these patients were more often exposed to diagnostic procedures with radiocontrast agent. This is supported by the fact that out of patients with chronic kidney disease that have not yet started dialy-

anginom pektoris, 18% bolesnika je preboljelo infarkt miokarda, dok je kod 35% dijagnosticirano srčano zatajivanje[2,3].

Iz obilja od preko tisuću recentnih studija o KIN tek njih devedesetak se može uzeti u ozbiljnije razmatranje nakon što se isključe irelevantni, eksperimentalni ili pregledni radovi, dok se tek dvadesetak randomiziranih studija s ukupno više od 3.000 uključenih pacijenata treba ozbiljno prihvatiti u metaanalizi[4]. Daljnjoj konsternaciji pridonosi i širina prikazanih incidencija KIN i to od 1% pa do 33%. Zamjetna je i diskrepanca pojave teških oblika KIN, liječenih dijalizom gotovo samo nakon kardioloških kateterizacija i izostanak klinički značajnih oblika nakon kontrastih CT procedura[5].

Jednostavna definicija KIN kao porast kreatinina za 25% i više od početne vrijednosti 24 do 72 sata nakon primjene kontrasta može objasniti navedenu diskrepancu, obzirom na kompleksnost kardioloških pacijenata kojima se vrše zahvati s uporabom kontrasta te protoku vremena u koji je događaj smješten, a tijekom kojeg pacijent prolazi kroz kaskade nepovoljnih fizioloških zbivanja.

U patofiziologiji nastanka KIN navodi se narušavanje bubrežne hemodinamike i hemoreologije mikrocirkulacije, osobito medularne kao posebno vulnerabilne, djelovanjem jodnog radiokontrasta na promjene tubularne tekućine uslijed porasta osmolaliteta i viskoznosti kontrastnog filtrata. Hiperosmolalna kontrastna sredstva imaju osmolalitet 1.400-1.800 mosmol/kg, hipoosmolalna 500-850 mosmol/kg, a izoosmolalna oko 290 mosmol/kg. Neosporno je i direktno citotoksičko djelovanje joda na stanice tubula i glomerula. Doza od 100 ml radiokontrasta koncentracije 300 mg I/ml sadrži 30 g joda. Taloženje proteinskog detritusa kao i precipitiranje uričke kiseline mogu dodatno oštetiti stanice bubrežnih tubula.

Na životinjskim modelima radioradiokontrast prvo izaziva vazodilataciju na koju se nadovezuje perzistentna i intezivna vazokonstrikcija, ali je uzrok vazokonstriktorne faze još nejasan[6].

Registrirane su razlike nastanka KIN obzirom na mjesto injiciranja radiokontrasta, pa je znatnija pojava nefropatije prilikom intraarterijske administracije, a i femoralni pristup je vulnerabiliniji u odnosu na radijalni. Vjeruje se da je to uslijed potrebe za većim volumenom kontrasta, kao i moguće embolizacije bubrežne mikrocirkulacije ateroskelotskim česticama kod već ranije ledirane stijenke arterija[7]. Neosporni su i potpuno jasni rizični čimbenici razvoja KIN kao što su to preegzistentna bubrežna lezija, pridružena šećerna bolest, visoki stupanj srčanog zatajivanja, visoka dob pacijenata, hipovolemija, veliki volumen radiokontrasta, istovremena terapija s ACE inhibitorima, nesteroidnim antireumaticima ili drugim poznatim nefrotoksinima. Ponavljanje pretrage unutar 72 sata donosi visoki rizik razvoja KIN[8]. Neospornu prednost pred hiperosmolalnim jodnim radiokontrastima ima uporaba onih hipoosmolalnih (ioheksol, iopamidol).

U kardiološkoj literaturi postoji pokušaj jednostavnog izračuna (risk-score) u predviđanju razvoja KIN te rizik za potrebom liječenja dijalizom. Navedeni alat je dostupan kao *Risk of Contrast-Induced Nephropathy Calculator*[9], a osnovni klinički rizični faktori za razvoj KIN kod pacijenata kod kojih se planira koronarografija i PCI su:

- sistolički arterijski tlak <80 mmHg;
- prisustvo intraarterijske balonske pumpe;
- srčano zatajivanje razreda NYHA III-IV ili anamneza ranijeg plućnog edema;
- životna dob viša od 75 godina;

sis treatment there are 16% of them with stable, 5% with unstable angina pectoris, 18% of patients suffered from myocardial infarction, and in 35% of them heart failure was diagnosed[2,3].

From the abundance of over a thousand of recent studies on CIN only some ninety of them can be taken into serious consideration after excluding irrelevant, experimental or review papers, while only some twenty randomized studies with a total of over 3.000 involved patients should be seriously accepted in the meta-analysis[4]. The scope of shown incidence of CIN from 1% to 33% contributes to further consternation. We can notice discrepancy between occurrence of severe forms of CIN, treated by dialysis almost only after cardiac catheterization and the absence of clinically significant forms after contrast CT procedures[5].

A simple definition of CIN as an increase in creatinine by 25% or more from the initial value from 24 to 72 hours after the application of the contrast agent can explain the above discrepancy considering the complexity of cardiac patients who undergo procedures where contrast agent is used and the flow of time in which the event is placed, and during which the patient goes through the stages of adverse physiological events.

The pathophysiology of CIN mentions impairment of renal hemodynamics and hemorrhology of microcirculation, particularly of medullary microcirculation being particularly vulnerable, by the effect of iodine radiocontrast agent on the changes in tubular fluid due to an increase in osmolality and viscosity of contrast filtrate. Hyperosmolar contrast agents have an osmolality 1400-1800 mosmol/kg, hypoosmolar contrast agents 500-850 mosmol/kg, and isoosmolar contrast agents about 290mosmol/kg. Direct cytotoxic effect of iodine on cells of tubules and glomeruli is indisputable. Dose of 100 ml radiocontrast agent concentration 300 mg I/ml contains 30 g of iodine. Deposition of protein detritus as well as precipitation of uric acid may further damage the cells of renal tubules.

In animal models radiocontrast agent first causes vasodilatation followed by a persistent and intense vasoconstriction, but the cause of vasoconstriction stage is still unclear[6].

The differences in occurrence of CIN considering the location of injecting the radiocontrast agent have been recorded, so any significant occurrence of nephropathy during intraarterial administration is greater, and the femoral access is more vulnerable compared to the radial access. It is believed that the reason is the need for a larger volume of contrast and potential embolization of renal microcirculation by atherosclerotic particles in previously impaired artery walls[7]. Completely clear risk factors for the development of CIN such as pre-existing renal lesions, associated diabetes, advanced class of heart failure, older age, hypovolemia, large volume of radiocontrast agent, concomitant therapy with ACE inhibitors, nonsteroidal anti-inflammatory drugs or other known nephrotoxins are undisputable. Repeating the test within 72 hours causes a high risk of developing CIN[8]. The use of those hypoosmolar contrast agents (iohexol, iopamidol) has undeniable advantage over hyperosmolar iodine radiocontrast agents.

In the cardiology literature, there is an attempt of making a simple calculation (risk score) in predicting the development of CIN and the risk of the need for dialysis treatment. The above mentioned score is available as Risk of Contrast-Induced Nephropathy Calculator[9]. According to it, the basic clinical risk factors for the development of CIN in patients planned for coronary angiography and PCI are:

- systolic blood pressure <80 mmHg;
- presence of intra-arterial balloon pump;

• vrijednosti hematokrita <0,39 kod muškaraca odnosno <0,35 kod žena;

• dijabetes;

• volumen kontrasta više od 100 ml;

• preegzistentno renalno oštećenje.

Prevencija bolusima infundirane izotonične tekućine izgleda smislena jer smanjuje vrijeme kontakta jodnog radiokontrasta sa stanicama bubrega čime se izbjegava direktna citotoksičnost, izbjegava se hipoksija i hipoperfuzija uslijed vazokonstrikcije, kao i snižavanje viskoziteta. Preporuka od 1 ml/kg/h fiziološke tekućine tijekom 6-12 sati je široko i s razlogom prihvaćena, prije i nakon postupka. Korekcija anemije uslijed ev. gubitka krvi nezaobilazna je u prevenciji nastanka KIN[10].

Nema jasnih pokazatelja koristi od preventivne uporabe bikarbonata, diuretika, a korištenje N-acetilcisteina je korisno u sprječavanju blagih oblika KIN, no ne može zaustaviti razvoj teških oblika bolesti. Antioksidantno djelovanje lijeka je limitirano, ali uslijed jednostavne primjene i niske cijene uputno ga je koristiti u dozi od 1.200 mg/dan prije izvođenja postupka, uz ponavljanje doze nakon provedene procedure. Statini su se i u ovom slučaju pokazali korisnim u prevenciji, najčešće se preporuča doza od 40 mg atorvastatina[11]. Pokušaji s antagonistima kalcijskih kanala, dopaminom, atrijskim natriuretskim peptidom, teofilinom ili fenoldopom nisu pokazali jasnu terapijsku učinkovitost[12].

Nametnula se potreba za uporabom drugih radiokontrastnih sredstava u smislu izbjegavanja KIN ili alergije na jod, pa se tako koristi gadolinij umjesto jodnih preparata, no uskoro se pokazalo da i ovaj radiokontrast može izazvati oštećenja bubrežnih funkcija.

Prvo izvješće o mogućoj povezanosti kontrasta koji sadrže ione gadolinija i njime izazvane nefrogene sistemske skleroze (NSS) bilo je prikazano 2006. godine[13]. Sindrom obuhvaća i fibrozu skeletne muskulature, pluća, testisa i miokarda i često je fatalan. Smatra se da je incidencija NSS 2,9%-4,0% i to isključivo u bolesnika s preegzistentnim oštećenjem glomerularne filtracije od >30 ml/min/1,73m^2, tj. u 4. stupnju kroničnog bubrežnog zatajenja, kao i u teškim oblicima akutnog bubrežnog zatajenja[14].

Budući da nema efikasne terapije za NSS, potrebno je izbjegavati izlaganje gadoliniju pacijenata s kroničnim bubrežnim zatajenjem te rabiti alternativne pretrage. U slučajevima potrebe preventivni pristup bi bio upotreba makrocikličkih kelata (gadoteridol), primjena najmanje moguće doze, izbjegavati ponavljanje pretrage, planirati provođenje hemodijalize nakon provedene pretrage kao i tijekom sljedeća dva dana za pacijente koji su već na dijalizi, iako nema jasno dokumentiranih pokazatelja da se tako sprječava NSS. Preporuka se bazira na farmakokinetici gadolinija očekujući korist od uklanjanja gadolinija dijalizom čiji je klirens >95%. Peritonejska dijaliza nije opcija uslijed njenog slabog klirensa[15].

Prema dostupnoj literuturi nisu znana bubrežna oštećenja inducirana uporabom iona željeza, mangana ili broma kao radiokontrasta.

Zaključno, kod pacijenata s kliničkim čimbenicima rizika za razvoj KIN poželjno je dnevno pratiti razinu kreatinina, ureje i kalija tijekom tri dana te ukoliko je porast ostatnih dušičnih substanci progresivan i prelazi 25% početne vrijednosti obvezno kontaktirati nefrologa. U prevenciji je preporučeno ordinirati 1ml/kg/h fiziološke tekućine tijekom 6-12 sati prije i nakon provedenog postupka, uz statine kao što smo naveli te ev. acetilcistein u dozi od 1.200 mg.

• heart failure of class NYHA III-IV, or history of previous pulmonary edema;

• age over 75;

• hematocrit value <0.39 in men or <0.35 in women;

• diabetes;

• contrast volume over 100 ml;

• pre-existing renal impairment.

Prevention by isotonic fluid bolus injection seems to be rational because it reduces the time of contact of iodine radiocontrast with kidney cells, thus avoiding direct cytotoxicity, hypoxia and hypoperfusion due to vasoconstriction, as well as lowering the viscosity. The recommendation of 1 ml/kg/h of saline solution during 6-12 hours is widely and reasonably accepted, before and after the procedure. Correction of anemia due to potential blood loss is unavoidable in the prevention of occurrence of CIN[10].

There is no clear evidence of the benefits of preventive use of bicarbonate, diurertics, while the use of N-acetylcysteine is beneficial in preventing mild forms of CIN, but cannot stop the development of severe forms of the disease. Antioxidant effect of the drug is limited, but due to a simple application and low cost it should be taken at a dose of 1,200 mg/d before conducting the procedure, repeating the dose after the procedure. Statins proved to be beneficial in prevention in this case as well, whereas the 40 mg dose of atorvastatin is the most commonly recommended dose[11]. Attempts with calcium channel blockers, dopamine, atrial natriuretic peptide, theophylline, or fenoldopam have not shown a clear therapeutic efficacy[12].

There is a need imposed for the usage of some other radiocontrast agents as to avoid CIN or allergies to iodine, so that gadolinium is used instead of iodine agents, but soon even this radio contrast agent proved to be causing kidney function impairment.

The first report on potential connection of contrast agents containing gadolinium ions and thus induced nephrogenic systemic sclerosis (NSS) was shown in 2006[13]. The syndrome includes the fibrosis in skeletal muscle, lungs, testicles and myocardium and it is often fatal. It is believed that the incidence of NSS is 2.9%-4.0% only in patients with pre-existing impairment of glomerular filtration rate of >30 ml/min /1.73m^2, i.e. at the stage IV of chronic renal failure, and in severe acute renal failure[14].

Since there is no effective therapy for the NSS, it is necessary to avoid exposing patients with chronic renal failure to gadolinium, so alternative tests should be applied. Should it prove to be necessary, a preventive approach would mean the use of macrocyclic chelate (gadoteridol), the application of the least possible dose to avoid repetition of the test, planning on conducting hemodialysis after the test performed and during the next two days for patients who are already on dialysis, although there is no clear documented evidence that NSS is thus prevented. The recommendation is based on pharmacokinetics of gadolinium expecting the benefit from the removal of gadolinium by means of dialysis, of which clearance is >95%. Peritoneal dialysis is not an option due to its low clearance[15].

Renal impairments induced by using ions of iron, manganese and bromine as radiocontrast agents are not mentioned in the literature we have at our disposal.

To conclude, it is desirable to monitor the level of creatinine, urea and potassium on a daily basis during the period of three days in patients with clinical risk factors for the development of CIN and if the increase in residual nitrogen sub-

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stances is progressive and exceeds 25% of the initial value, a nephrologist is to be consulted. In prevention it is recommended to prescribe 1ml/kg/h of saline during the 6-12 hours before and after the procedure, with statins as indicated above, and acetylcysteine as required in a dose of 1.200 mg.

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