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Evaluation of the Efficacy of Fenoldopam in the Prevention of Contrast-Induced Nephropathy (CIN) by Neutrophil Gelatinase-Associated Lipocalin (NGAL)

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Abstract

Background: Contrast media induced nephropathy (CIN) is defined as a reduction in renal function induced using contrast media in radiology. Various strategies and drugs have been applied to prevent CIN.

Aims: The aim of this study was to evaluate the efficacy of Fenoldopam versus hydration, in reducing the CIN incidence.

Methods: Open, non-randomized trial. Efficacy was evaluated using renal function indicators and NGAL.

Results: Despite the bias of the type of study (non-randomized), the results obtained (to be subjected to further verification), showed an improvement in the values of creatininemia and NGAL at 72 hours in the Fenoldopam group.

Conclusions: These preliminary data should be supported by a larger series.

Keywords: CIN, Contrast media toxicity, Acute Renal Failure, Fenoldopam, NGAL

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INTRODUCTION

Contrast media induced nephropathy (CIN) is defined as a reduction in renal function due to its administration. This implies damage occurring within three days of exposure and is quantified as an increase of at least 25% in serum creatinine in the absence of an alternative etiology (1). CIN is the third leading cause of hospital acquired nephropathy. CIN has a low incidence in patients with normal renal function, from 0 to 5% (1-3) but this increases in presence of a low renal functional reserve. An incidence between 12 and 27% has been reported in some prospective studies (1,2,4); in particular, in a population affected by diabetic nephropathy undergoing coronary angiography, the incidence of CIN was estimated to be around 50% despite the use of low osmolarity contrast media and adequate hydration, requiring the use of dialysis in 15% of affected patients (5). Moreover, in animal studies the use of high molecular weight contrast agents would seem to accentuate hypertension-induced glomerulosclerosis (6).

Risk factors

The severity of pre-existing renal insufficiency is the major risk factor for the development of CIN, especially in the case of diabetic nephropathy (1,4). The use of large volumes of contrast media (CM) and repeated doses (72 hours) also play a fundamental role in the development of this pathology, as well as the intra-arterial use versus the venous one. Dehydration and all conditions of impaired renal perfusion increase the risk of CIN. Advanced age is an important risk factor due to impaired renal function and perfusion. The use of NSAIDs, aminoglycosides and other nephrotoxic substances by themselves also promote the development of the pathology in question.

The type of contrast agent used is also important: those with high osmolarity are undoubtedly more toxic (3,4,7). A multicenter study demonstrates that anionic dimers are less nephrotoxic than low osmolarity anionic monomers (8).

Pathophysiology

Both reduction of renal perfusion and direct toxic effects on tubular cells are implicated in the pathophysiology of contrast agent nephrotoxicity.

Once the contrast agent molecules have been injected by crossing the membranes of the capillaries, they are distributed in the extracellular space, and vice versa, reaching a state of equilibrium after about 2 hours. Only less than 1% is eliminated extra renally, while the glomeruli continuously filter these molecules. In patients with preserved renal function, the half-life of the contrast medium is approximately 2 hours and 98% of the injected dose is excreted after 24 hours (9,10).

Since these molecules are not reabsorbed by the tubules, they exert a powerful osmotic effect which opposes the reabsorption of water and salts attempted by the renal tubules, finally causing natriuresis. This resembles the mechanism of action of osmotic diuretics, and how they stimulate Tubuloglomerular feedback (TGF). The increase in the filtrate results in an increase

in intratubular pressure which counteracts the intraglomerular pressure resulting in a reduction in the glomerular filtration fraction (GFR). The TGF, determined in response to natriuresis, determines the vasoconstriction of the glomerular afferent arteriole, further reducing the GFR with a notable increase in renal vascular resistance. In this mechanism, endothelin and adenosine synthesized directly by the renal tubules play a fundamental role (11,12). (Figure 1)

peak is generally evident 3/4 days after administration of the contrast medium. Moderate proteinuria and oliguria may be associated. Most patients with CIN do not develop oliguria except those with pre-existing renal impairment. Usually, these episodes are self-limiting in about one or two weeks but sometimes they can develop non-renal complications such as sepsis, bleeding and respiratory failure or precipitate comorbidities and significantly increase

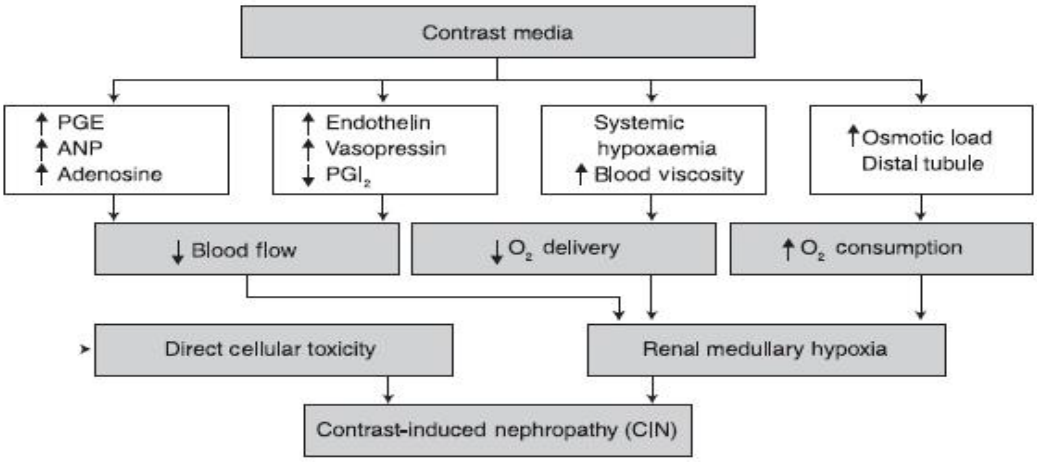


Figure 1. Etiopathogenesis of CIN

Furthermore, tubular obstruction by Tamm-Horsfall proteins could also play a role in the development of nephropathy but there is little evidence in this regard (9). Toxic effects on the renal tubules, on the other hand, include vacuolization of the epithelium, DNA fragmentation and necrosis of the thin part of the ascending loop of Henle of the renal medulla (1,3). CIN is clinically characterized by a reduction in the glomerular filtration fraction (GFR) which is manifested by an increase in serum creatinine and a reduction in clearance; the hospitalization (2). Laboratory evaluation of CIN was based on serial determination of serum creatinine and its clearance to estimate GFR. But creatinine is not a reliable marker since it is both filtered by the glomeruli and secreted (from 10 to 40%) by the tubules and its concentration can vary according to the muscle mass, diet, age, and sex of the patient. Blood urea nitrogen is equally unreliable in determining GFR. Recently, new markers have been introduced to evaluate renal function early. Among these, NGAL (neutrophil gelatinase-associated lipocalin) and cystatin C

appear to be extremely promising (14). NGAL secretion occurs in response to renal tubular stress, anticipating the serum creatinine peak by up to 24 h. Normal values in urine for adults are considered 1.0-20.0 ng/ml while in serum 70-105 ng/ml. This 21 kDa protein is synthesized partly locally by the distal nephron and partly systemically in response to renal damage. This molecule has a bacteriostatic and antioxidant action, through the bond with iron ions, but it would also seem to act as a growth factor in regulating apoptosis; it can be detected both in the urine (early) and in the blood. It binds to the siderophores secreted by the bacteria, removing them, and thus limiting their growth; but it also binds to human siderophores limiting the production of ROS (reactive oxygen products) (15). In patients who developed CIN with previous normal renal function, NGAL levels increase already after 2 hours (urine), and after 4 hours in serum, while the creatinine peak was revealed to be statistically significant only after 48 hours (12).

CIN prevention

Various protocols have been studied and adopted to prevent CIN. Volume expansion and the use of low osmolarity contrast media have proved to be the most effective of these (1, 4, 12, 16); volume expansion should be started 4 hours before the procedure with 0.9% NaCl at 100 mL/h until 24 hours after the use of contrast media (16).

Hydration

Adequate peri-procedural hydration is the key component to preserving renal function in patients undergoing contrast medium administration. The goal is to maintain a sufficient intravascular volume to increase renal perfusion, establishing an adequate diuresis before exposure to contrast media. The protective effect was first established by Solomon et al. in a study of 78 patients with CRF subjected to angiography, in which it emerged that those who were hydrated with 0.45% saline had a lower incidence of CIN than those who also added the infusion of mannitol and furosemide to hydration. There is no unanimous consensus about the appropriate mode of hydration (oral vs parenteral). Some studies showed that enteral and intravenous administration had similar protective effects. But in a study by Trivedi (16,17), enteral fluid administration was associated with a 10-fold greater risk of developing CIN versus the intravenous group. In a study by Mueller (18) isotonic hydration was superior in reducing CIN rates compared to hypotonic.

In the OTHER CAN study (19), in 63 patients undergoing percutaneous coronary revascularization, continuous fluid administration resulted in a lower incidence of CIN than in the bolus hydration group. There are

no unique standards regard the hydration of patients undergoing contrast media. But it should be kept in mind that certain subpopulations of patients, such as those with impaired left ventricular function or chronic renal failure, require cautious hydration. One of the most common hydration regimens recommends 1ml/kg/h of saline solution 12 hours before and after in presence of normal ventricular function, while in those with reduced ejection fraction the volume to be infused should maintain the euvolemic state, balancing the diuresis in the previous and following 12 hours.

According to the European guidelines of myocardial revascularization, all patients with chronic renal failure should receive hydration with saline at least 12 before and 24 hours after the procedure to reduce the risk of CIN and the amount of contrast medium should not exceed 4 ml/kg (20).

Use of sodium bicarbonate

Urine alkalinization with sodium bicarbonate is thought to reduce contrast agent-induced renal damage by reducing pH-dependent free radicals. However, various studies on the subject have shown conflicting conclusions (21).

Forced diuresis

Intense hydration combined with the use of diuretics has the aim of determining and maintaining a high urinary excretion, allowing the elimination of the contrast medium, and reducing its toxic effects. The results of the various studies are contrasting; in some the administration of diuretics it highlighted harmful effects by increasing the incidence of CIN probably, due to the increase in oxygen consumption by the nephron using some types of drugs (Furosemide e.g.) (16).

Pharmacological agents for the prevention of CIN:

N-acetylcysteine

Various studies have investigated the ability of the antioxidant containing thiol groups to prevent the appearance of CIN. The APART trial demonstrated a lower incidence in the group treated with acetylcysteine versus hydration alone (8% vs 45%) but many other studies have not confirmed this ability, including the large randomized study of the American Heart Association in 2010 (22-24).

Dopamine

Decreased renal blood flow due to vasoconstriction is an important determinant of the development of CIN. Low-dose dopamine has a dilatory effect on renal vessels and may have a nephroprotective effect. However, studies have failed to demonstrate a protective effect from the development of CIN, and indeed dopamine use has been related to the severity and duration of renal damage developed (25,26).

Other Drugs and protocols

The preventive use of furosemide and mannitol is not recommended in the guidelines; the use of theophylline and calcium channel blockers remains uncertain, as does the use of acetylcysteine, which has been ineffective in

some studies. Moreover, hemodialysis does not seem to protect the residual renal function from the action of the contrast medium (1,11,13).

Fenoldopam

Fenoldopam is a selective DA1 dopamine receptor agonist that increases renal plasma flow. In the randomized CONTRAST trial with CKD patients undergoing angioplasty the use of fenoldopam failed to decrease the incidence of CIN (33% vs 30%) while in another trial the incidence was halved (21% vs 41%) Recently, the use of fenoldopam has been shown to reduce the incidence of CIN in patients with poor renal function reserve undergoing coronary angiography (but further studies are needed to evaluate its real efficacy (27). Fenoldopam mesylate is a benzazepine derivative with a potent but short agonist action at the dopamine A1 receptor and moderate affinity for α2 receptors, zero for DA2 receptors; it decreases systemic resistance and increases renal blood flow (28,29). Given the poor solubility in lipids, it does not cross the blood-brain barrier and therefore has no effects on the central nervous system when it is infused intravenously. Infused at a rate of 0.01-1.6 mcg/kg/min, it reaches steady state in 20 minutes (half-life T1/2 9.8 minutes). In plasma, 85-90% of the drug is bound to proteins. Elimination, predominantly renal (90%), is not influenced by sex, race, weight, age. Various studies have validated the use of fenoldopam during hypertensive emergencies by comparing it with drugs already used such as nitroprusside, esmolol, nicardipine. Most of the adverse effects attributed to fenoldopam are related to the vasodilator action. These include headache, flushing, dizziness, tachycardia, or bradycardia (30). Fenoldopam increases intraocular pressure, and this has been attributed, at least in part, to decreased aqueous humor drainage. This effect is more pronounced in patients with intraocular hypertension. Therefore, fenoldopam should be used with caution in patients with glaucoma (31). Since the discovery of dopamine's renal actions, its use as a renal protector in clinical circumstances that could endanger renal function, such as vascular surgery and shock, has become common practice, despite the lack of solid evidence. The scientific evidence of fenoldopam in this sense, together with laboratory data are encouraging, although data from clinical use are still vague. In rats, the nephrotoxicity induced by antibiotics (amphotericin B, cyclosporine) would seem to be attenuated by the administration of fenoldopam. In dogs, the use of fenoldopam may protect the kidneys from the development of contrast-induced nephropathy (32). In mechanically ventilated patients with polytrauma, the use of fenoldopam would improve renal perfusion, natriuresis and improve the survival of patients undergoing thoraco-abdominal aneurysm repair (33). In a recent clinical trial, fenoldopam appears to increase splanchnic blood flow in patients with septic shock (34,35).

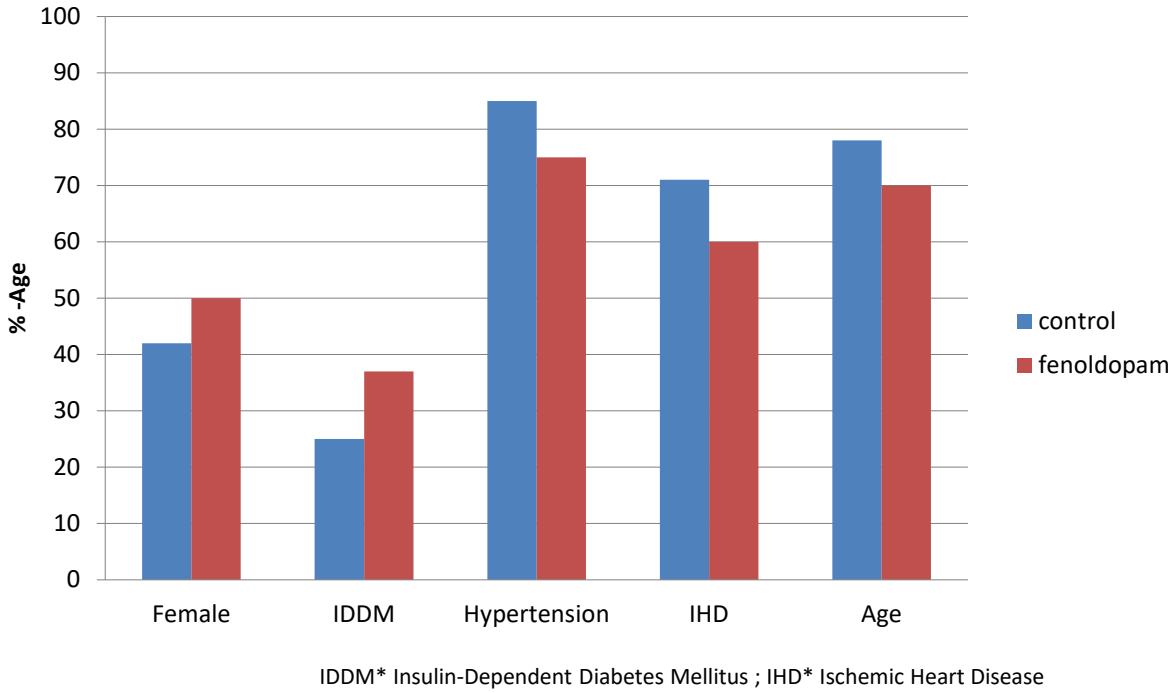
AIMS

Aim of this study is to evaluate the efficacy of fenoldopam to reduce the incidence of CIN in patients with normal/increased risk, via the evaluation of traditional markers of renal function (creatinine e.g.) and the dosage of NGAL, at 24 and 72 hours from exposure to the contrast media. The prospective non-randomized study was conducted at the University of Rome Tor Vergata, Rome, Italy, in the period 2019-2020.

MATERIALS AND METHODS

The cohort was represented by 16 patients, homogeneous for qualitative and demographic characteristics (Figure 2). All patients had diabetes mellitus; some on insulin treatment (IDDM) and all enrolled for lower limb angioplasty (diabetic foot); the presence of arterial hypertension and ischemic heart disease should also be noted. The exclusion criteria included hemodynamic instability, heart failure conditions, renal failure treated with hemodialysis and other known renal diseases (glomerulonephritis, single kidney patients, polycystic kidney, renal artery stenosis) (30). Patients were adequately informed about the study; After agreeing to take part, a consent form was signed. All patients were over 60 years of age, and all had plasma creatinine values greater than 1.2mg/dl. Group A, (n8), was treated with fenoldopam in continuous infusion 0.05 mcg/kg/min for 24 hours, plus NaCl 0.9% 100ml/h. The infusion started 30 minutes before the start of the radiological procedure. Group B (n8), was treated only with I.V hydration with 0.9% NaCl 100 ml/h. The infusion began 30 minutes before the start of the radiological procedure and continued for 24 hours. For the entire cohort, radiological procedural time, type, and amount of contrast agent used were considered. After 24 and 72 hours from the procedure the values of creatinemia, serum NGAL as well as blood pressure and heart rate values were examined. Any patient-reported adverse event or clinical complication was noted, as well as the days of hospitalization. The entire cohort of patients was observed to determine the incidence of CIN (increase in serum creatinine of 25% compared to baseline), both in all cases and in relation to age, pre-procedural creatinine values, and to the quantity of contrast medium used. The evaluation of the NGAL value was obtained by peripheral venipuncture in a tube with EDTA (lavender cap) to be then analyzed using the Alere Triage NGAL kit. Since the test kit is unable to determine NGAL values lower than 60 ng/ml, this will be the minimum value assigned whenever the machine measures a value of “<60ng/ml”.

Statistical analysis of the data obtained was performed using Student's T-test, with a significance threshold of $p<0.05$.



IDDM* Insulin-Dependent Diabetes Mellitus ; IHD* Ischemic Heart Disease

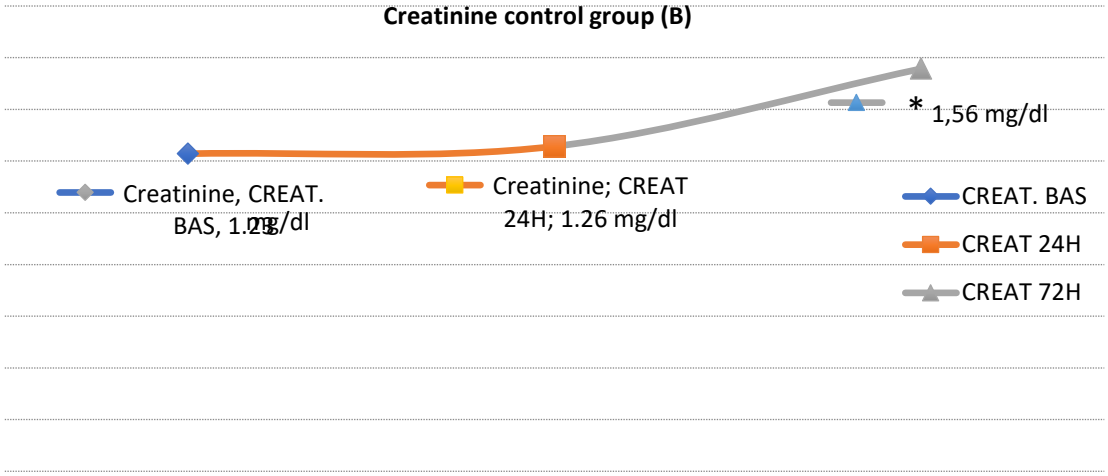
Figure 2. Demographic characteristics and risk factors in the cohort

The dosages of creatinine and NGAL showed important differences in the two groups, although the small number does not allow a reliable statistical evaluation. Analyzing the data relating to creatinine as a whole, this, in the control group, increased at 72 hours, (the time limit for the diagnosis of CIN), by 26% compared to the baseline value (Graph 1).

This increase is almost at the limit of statistical significance. The incredibly high figure would make the incidence of CIN remarkable in the group studied but this, in truth, is due to a patient who reported an increase of 175%, who also died, due to pulmonary complications in the ward a few days later the procedure. Along with this case, another patient showed a 25% increase; therefore, a diagnosis of CIN could be made in 2 of the enrolled patients, with a conceivable incidence of 25% (2/8), which has already been encountered

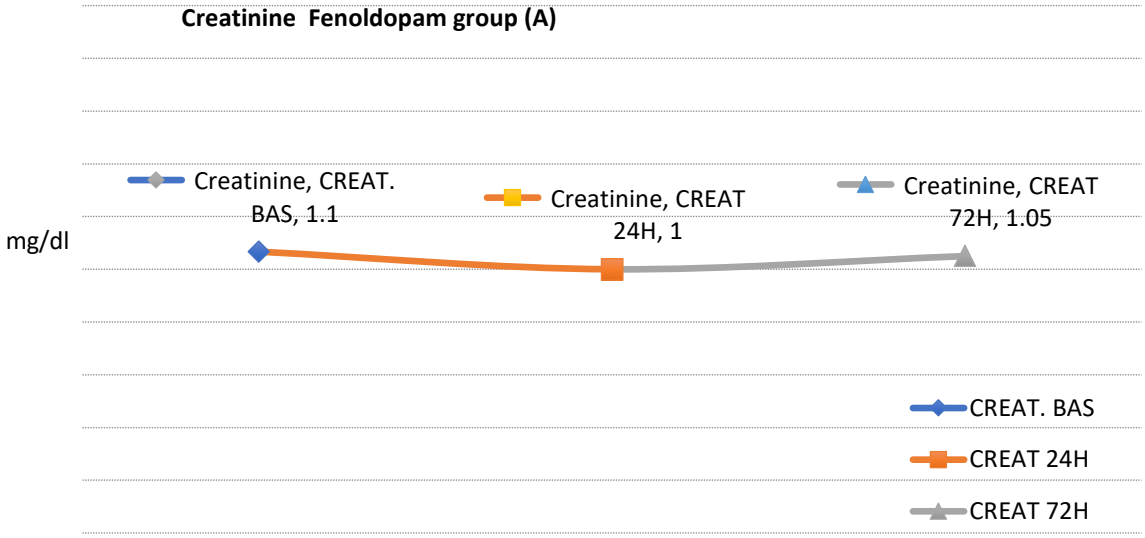
in other studies. At 24h, creatinine showed an almost zero increase of 2.5%, confirming the poor reliability of this marker in early diagnosis.

With regards to the dosage of NGAL in the control group (B) (Graph.3), an average increase of 15% was noted at 24 hours, and of 76% at 72 hours. The increase at 72 h reached a statistical significance of $p<0.05$. Again, this value is forced by the extremely high 471% increase in the deceased patient. However, one patient who had

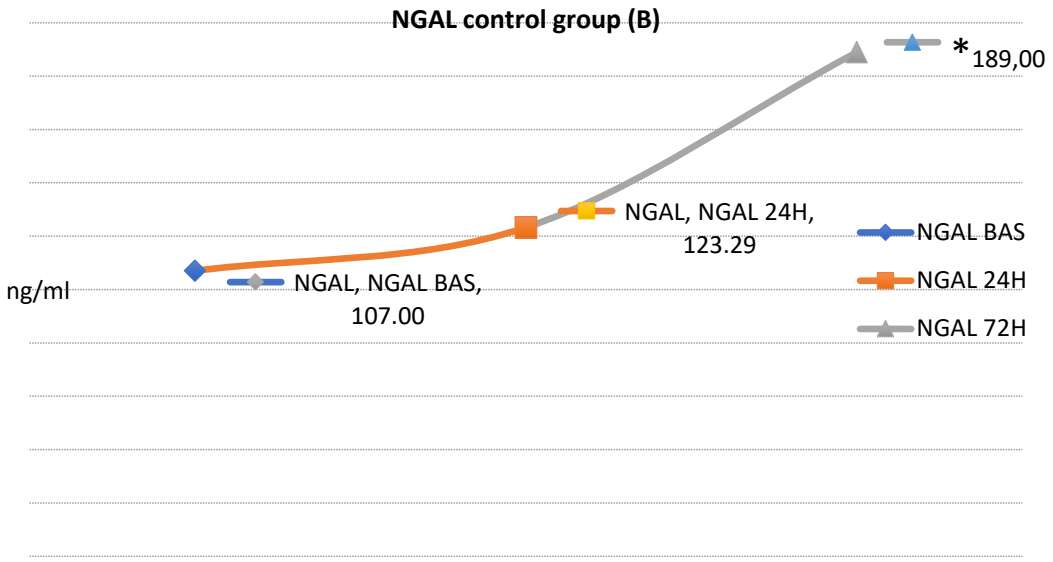


Graph 1. Average creatinine values of the control group (B) at 24 and 72 hours. ($p<0.05$)

In the fenoldopam group (A), creatinine remained almost stable compared to the baseline values, which were, however, lower than control group (Graph 2).



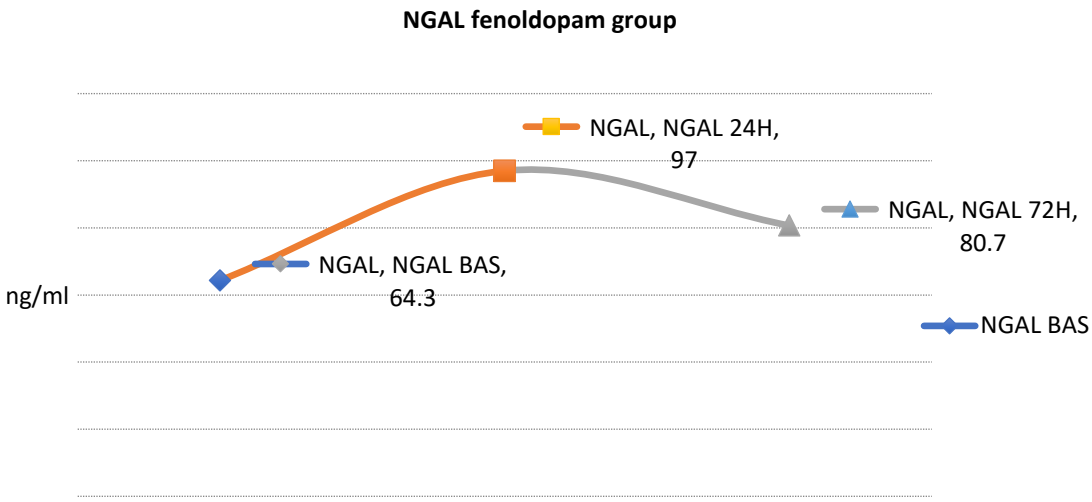
Graph 2. Average values of creatinine levels in Fenoldopam group (A)



Graph 3. Mean values of NGAL of the control group at 24 and 72 hours (*p<0.05)

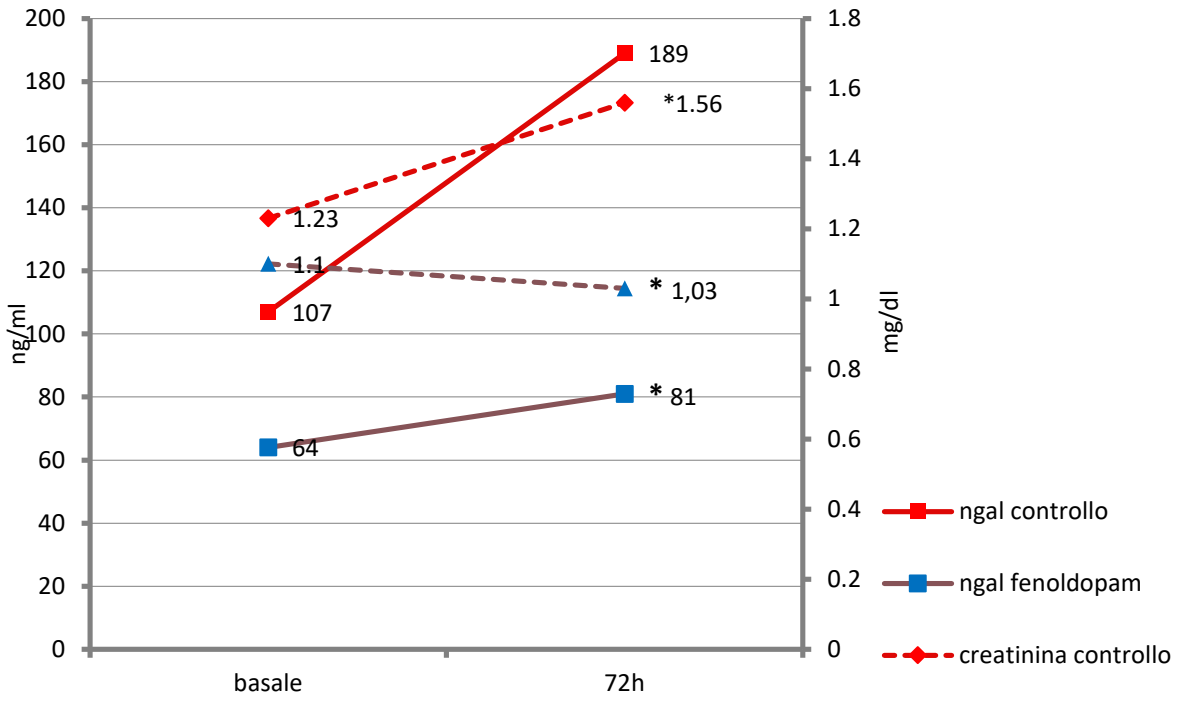
only a 15% increase in creatinine showed a 287% increase in NGAL while another whose creatinine had increased by 12.5% showed an increase in NGAL by 30.1%, demonstrating the incomplete inter independence of the two markers.

Regarding group A (fenoldopam) the dosage of NGAL, which was also lower in baseline values than the controls, showed an increase of 51% at 24 hours and of 26% at 72 hours, considerably lower than in the untreated group. (Graph.4)



Graph 4. Mean values of NGAL of the group treated with fenolopam

quantification of the contrast medium used for the



Graph 5. Comparison of the increases at 72h of creatinine and NGAL of the two groups studied. * p<0.05

DISCUSION

Despite the incomplete strength of the evidence shown in the literature regarding the efficacy of fenoldopam in the prevention of CIN, our preliminary results obtained showed an improvement in the values of creatininemia and NGAL at 72 hours in group A. These preliminary data should be supported by a larger series, which could increase the already highlighted significance of the decreased dosages at 72h of creatinine and NGAL compared to the group of control patients (B). Furthermore, the two groups showed an almost linear trend at 24 and 72 hours, recalling that the risk factors were almost similar in quality and distribution. A bias was the procedures, as it is often diluted by the operator directly at the angiography table, making the final calculation difficult (36). It is important to remember that CIN is a subclinical syndrome and as such often does not show itself in a striking way. In fact, these differences in the dosage of the markers highlighted between the two groups do not have a clinical correlation but should be the representation of a parenchymal damage that has occurred, which in patients with sufficient functional reserve do not turn into a clinical equivalent. It should also be noted that in three of the control group patients studied, NGAL showed increases that either were not shown by the creatinine dosage or were more evident. None of

the patients in the fenoldopam group showed signs of heart failure or alteration of the clinical course attributable to adverse effects of the drug.

CONCLUSIONS

Our preliminary data showed the efficacy of fenoldopam in peri-procedural continuous infusion in preventing the increase in markers of renal damage following the use of iodinated contrast medium. Furthermore, a clinical follow-up would be useful to highlight the medium and long-term clinical impact. If the benefit refers only to the laboratory panel, we should ask ourselves whether the use of a drug as powerful as it is expensive justifies its adoption. Moreover, it was not always possible to evaluate the correct hydration of the patient before and after the radiological procedure, a practice which now has shown the greatest efficacy in reducing the incidence of CIN in the literature.

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Conflict of Interest Statement: The authors declare that they have no conflict of interest.

REFERENCES

1. Morcos SK, Thomsen HS, Webb JAW, and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR). Contrast media induced nephrotoxicity: a consensus report. Eur Radiol 1999; 9:1602–1613.

2. Solomon R. Contrast medium-induced acute renal failure. Kidney Int 1998; 53:230–42.

3. Berns AS. Nephrotoxicity of contrast media. Kidney Int 1989; 36:730–40.

4. Rudnik MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. Kidney Int 1995; 47:254–61.

5. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 1990; 89:615–20.

6. Duarte CG, Zhang J, Ellis S. The SHR as a small animal model for radiocontrast renal failure. Relation of nephrotoxicity to animal's age, gender, strain, dose of radiocontrast. Renal Failure 1997; 19:723–43.

7. Morcos SK. Contrast media-induced nephrotoxicity—questions and answers. Br J Radiol 1998; 71:357–65.

8. Aspelin P, Aubry P, Fransson S-G, Strasser R, Willenbrock R, Berg KJ for the NEPHRIC study investigators. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003; 348:491–9.

9. Thomsen HS, Morcos KS.Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) Guidelines. The British Journal of Radiology, 76 (2003), 513–518.

10. Bourin M, Jolliet P, Ballereau F. An overview of the clinical pharmacokinetics of x-ray contrast media. Clin Pharmacokinet. 1997; 32:180–193.

Moore, Bellomo, Nichol. Biomarkers of acute kidney injury in anestesia, intensive care and

major surjery. Minerva Anesthes . 76 (6) 2010:425-40.

11. Side Effects of Radiographic Contrast Media: Pathogenesis, Risk Factors, and Prevention Michele Andreucci, 1Richard Solomon, 2and Adis Tasanarong3 BioMed Research International Volume 2014, Article ID 741018, 20 pages http://dx.doi.org/10.1155/2014/741018

12. Ling W, Zhaoui N, Ben H, Leyi G. Urinary IL-18 and NGAL as early predictive biomarkers in contrast – induced nephropathy after coronary angiography. Nephron (2008)108: 176-81.

13. Thomsen HS. Contrast nephropathy. In: Thomsen HS, Muller RN, Mattrey RF, editors. Trends in contrast media. Berlin: Springer Verlag, 1999;103–16.

14. He Y, Deng Y, Zhuang K, Li S, Xi J, Chen J (2020) Predictive value of cystatin C and neutrophil gelatinase-associated lipocalin in contrast-induced nephropathy: A meta-analysis. PLoS ONE 15(4): e0230934. https://doi.org/10.1371/journal. pone.0230934

15. Moore, Bellomo, Nichol. Biomarkers of acute kidney injury in anestesia, intensive care and major surjery. Minerva Anesthes . 76 (6) 2010:425-40.

16. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol and furosemide on acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331:1416–20.

17. Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron Clin Pract. 2003;93(1):C29–C34.

18. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med. 2002;162(3):329–336.

19. Krasuski RA, Beard BM, Geoghagan JD, Thompson CM, Guidera SA.Optimal timing of hydration to erase contrast-associated nephropathy: the OTHER CAN study. J Invasive Cardiol. 2003;15(12):699–702.

20. 2018 ESC/EACTS Guideline.s on myocardial revascularization. European Heart Journal (2019) 40, 87–165 doi:10.1093/eurheartj/ehy394

21. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine. The New England journal of medicine 2018; 378:603-14.

22. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). Am J Cardiol. 2002; 89:356-358.

23. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med. 2000;343:180-184.

24. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy

Trial (ACT). Circulation. 2011, 13;124(11):1250-9.

25. Kapoor A, Sinha N, Sharma RK, et al. Use of dopamine in prevention of contrast induced acute renal failure—a randomised study. Int J Cardiol. 1996; 53:233-236.

26. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. Am J Cardiol. 1999; 83:260-263, A5.

27. Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am Heart J. 2002;143(5):894–903.

28. Mathur VS, Swan SK, Lambrecht LJ, et al: The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. Crit Care Med 27:1832-1837, 1999

29. Singer I, Epstein M: Potential of dopamine A-1 agonists in the management of acute renal failure. Am J Kidney Dis 31:743-755, 1998

30. Fenoldopam: selective peripheral dopamine receptor agonist for the treatment of severe hypertension. M.Murphy,C.Murray, G. Shorten, N Engl J Med, Vol. 345, No. 21

31. Everitt DE, Boike SC, Piltz-Seymour JR, VanCoevorden R, Audet P, Zariffa N, Jorkasky D. Effect of intravenous fenoldopam on intraocular pressure in ocular hypertension. J Clin Pharmacol. 1997 Apr;37(4):312-20. doi: 10.1002/j.1552-4604. 1997.tb04308. x. PMID: 9115057.

32. Duarte CG, Zhang J, Ellis S. The SHR as a small animal model for radiocontrast renal failure. Relation of nephrotoxicity to animal's age, gender, strain, dose of radiocontrast. Renal Failure 1997; 19:723–43.

33. Sheinbaum R, Safi H, Ignacio C, Carter J, Reyna R. Renal protectionand improved outcome by utilization of a DA-1 agonist (fenoldopam) in TAAA repair. Anaesth Analg 2000;90: Suppl: SCA31. abstract.

34. Morelli A, Rocco M, Conti G, et al: Effects of short-term fenoldopam infusion on gastric mucosal blood flow in septic shock. Anesthesiology 101:576-582, 2004.

35. Noce A, Marrone G, Rovella V, Busca A, Gola C, Ferrannini M, Di Daniele N. Fenoldopam Mesylate: A Narrative Review of Its Use in Acute Kidney Injury. Curr Pharm Biotechnol. 2019;20(5):366-375. doi: 10.2174/1389201020666190417124711. PMID: 31038062; PMCID: PMC6751352.

36. Jean-Sebastien Rachoin, Yanika Wolfe, Sharad Patel & Elizabeth Cerceo (2021) Contrast associated nephropathy after intravenous administration: what is the magnitude of the problem?, Renal Failure, 43:1, 1311-1321, DOI: 10.1080/0886022X.2021.1978490