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CONTRAST-INDUCED NEPHROPATHY: A PROSPECTIVE STUDY IN 66 CRITICALLY ILL PATIENTS.

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ABSTRACT

Introduction: radiocontrast-induced nephropathy is defined by an increase in serum creatinine of 44,2 µmol/l (or 0,5 mg/dl) or a relative increase of 25% from the base of creatinine occurring 48 to 72 hours after intravenous administration of iodinated contrast media. It remains a common cause of acute renal failure in intensive care at the origin of specific morbidity and mortality. Prevention is therefore required, especially in patients with risk factors for kidney failure and uses a variety of protocols. Materials and Methods: This is a randomized longitudinal observational study over a period of six months from July 2014 to December 2014. Inclusion criteria were the need to conduct an examination with injection of iodinated contrast material with occurrence of acute renal failure or worsening of pre-existing renal insufficiency. Exclusion criteria were all patients with dialysis formal indication.The authors evaluate a renal protection protocol in 66 intensive care patients. This population was randomized into 2 groups: Group P1 which benefited from an hydro electrolytic and metabolic equilibration and P2 group who participated in addition to that a urine alkalinization before, during and after injection of iodinated contrast media. The alkalizing protocol uses sodium bicarbonate 1.4%: 3 ml / kg administered one hour before the injection of the iodinated contrast media and 1 ml/kg /h for 6 h after. Results: The mean age was 53.51 ± 14.28 years, ranging from 19 to 87 years. The sex ratio is 0.53. Hypovolemia and shock states were renal failure risk factors most frequently encountered (56.1 and 36.4% respectively). The diabetes represents 16.7% and a pre-existing renal disease was observed in 12.12%. The mean initial creatinine was 138 ± 36.6 mmol / l with a range from 62 to 333 mmol /l.7 patients from the P1 group (21.8%) and 4 patients from the the P2 group (11.7%) have developed an acute renal failure during the 4 days of the monitoring of serum creatinine. The use of dialysis was required in a patient or 3.12% for P1, vs 0% for P2. This work highlights accordance with literature data the nephroprotective role of alkalizing urine pre per and post procedure. In multivariate analyze some independent factors predictive of the occurrence of acute renal failure induced by iodinated contrast media were identified. There is a creatinine clearance <60 ml/min/1.73 m2 (OR = 1, 07 p <0.08), intra-arterial injection (OR = 1.07 p <0.15), a quantity of iodinated contrast media.> 120 ml (OR = 1.62 p <0.15) and SAPS II> 30 (OR = 1.07 p <0.08). Conclusion: Radiocontrast-induced nephropathy is unanimously recognized as a major cause of hospital acute renal failure. The

intensivist plays an important role in the implementation of preventive measures to address the risk factors related to the patient. The radiologist should a reasonable iodinated contrast media use.

Key words: Iodinated contrast media - Acute kidney injury - Intensive care unit - Risk factors - Sodium bicarbonate.

INTRODUCTION

Nephropathy to iodinated contrast media (NPC) is the 3rd cause of IRA acquired in the hospital after acute renal failure (ARF) Functional and drug causes. [1]
Its occurrence in intensive care is a common situation. Radiological exploration may require iodinated contrast injection products (PCI) and be, cause a worsening of renal function, responsible for own mortality and a lengthening of the duration of stay in intensive care. The IRA usually regresses, and rarely requires dialysis. [2] It increases morbidity and mortality, hospital stay time and can lead to end-stage renal failure with need for dialysis. It is an independent mortality factor.
Preventive measures are therefore necessary in these patients at risk.

MATERIALS AND METHODS

This work evaluates a kidney protection protocol by alkalinization of urine before, during and after PCI injection in critically ill patients, comparing it to a control group to prevent the occurrence of NPC in critically ill patients. This is a randomized longitudinal observational study over a period of six months from July 2014 to December 2014. The inclusion criteria were the need to conduct an examination with injection of iodinated contrast material with occurrence of acute renal failure or worsening of pre-existing renal insufficiency. Exclusion criteria were all patients with a formal indication dialysis (chronic renal impairment, hyperkalemia, severe acidosis).
She has focused on a cohort of 66 patients. The items collected prior procedure were age, sex, ethnicity (necessary for the calculation of creatinine clearance using the formula CKD ear), patient history, creatinine, hemoglobin and other biochemical parameters required for the calculation of the SAPS II. Patients were divided into two groups: The first group P1 (control), or goals of resuscitation are maintaining an optimal state of hydration, adjusted for any pre metabolic abnormalities, per and post procedure. No other specific preventive measures were recommended. The second group P2 (Bicar) consists of an intravenous fluid coupled with a urine alkalinization with isotonic sodium bicarbonate 1.4%: 3 ml / kg administered one hour before the injection of PCI followed by 1 ml / kg / hr and 6h after injection. The ICP used was in all cases * Iohexol OMNIPAQUE administered by automatic syringe for all patients. The comparison of two groups based on the collection and comparison of creatinine and calculation of clearance by CKD ear to j + 1, j + 2, j + j + 3 and 4 after PCI injection.
Quantitative variables were expressed as means ± standard deviation and qualitative variables as frequencies. Chi 2 of Pearson's test was performed to compare the observed frequencies. The comparison of average parameters P1 and P2 groups was performed by the test (t) Student. Statistical significance was defined as $p < 0.05$. Statistical analysis is performed on the IBM SPSS statistics software V 20.0.

RESULTS AND DISCUSSION

66 patients were included in this study. The mean age was 53.51 ± 14.28 years with extremes ranging from 19 to 87 years. The sex ratio is 0.53.

Hypovolemia, found in 37 patients or 56.1% and shock conditions in 24 patients or 36.4% were renal failure risk factors most frequently encountered. 11 patients were diabetics and 16.7% a pre-existing renal disease was noted in 8 patients was 12.12%.

The mean baseline serum creatinine was 138 ± 36.6 mmol / l, with a range of 62 to 333 mmol / l (Table I).

Data	N = 66
Age in years	53,51 ± 14,28
Male n (%)	35 (53)
SAPS II score	22 ± 3
Diabetes n (%)	11 (16,7)
Nephropathy n (%)	8 (12,12)
Hypovolemia n (%)	37 (56,1)
State of shock n (%)	24 (36,4)
Nephrotoxic drugs n (%)	21 (27,5)
Creatinine (mmol / l)	128 ± 26,6 µmol/l

Table I: Characteristics of the study population.

Detailed patient characteristics P1 and P2 groups are reported in Table II. Patients whose procedure was complicated by kidney failure induced or aggravated by ICP injection 21.8% in the P1 group (7 patients) against 11.7% in the P2 group (4 patients). These are mainly those whose GHI score is above 24, those with impaired renal function previously with a greater frequency of shock (including hemorrhagic). In this group, the procedure was performed willingly emergency. Patients with a clearance baseline creatinine less than 60 ml / min / 1.73 m2 (clearances are respective mean 56 ± 24 ml / min / 1.73 m2 and 62 ± 29.5 ml / min / 1.73 m2 for P1 and P2).

Data	P1 (Witness)	P2 (Besar)	value p
	N=32	N = 34	
Age in years	52,9 ± 13.88	54,12 ± 17.13	0,75
Male n (%)	17 (53)	18 (52,9)	0,73
SAPS II score	23 ± 2	21 ± 3	0,90
Diabetes n (%)	6 (18,7)	5 (14,7)	0,95
Nephropathy n (%)	4 (12,5)	4 (11.7)	0,98
Hypovolemia n (%)	19 (59)	18 (53)	0,60
State of shock n (%)	11 (34,5)	13 (38,2)	0,10
Nephrotoxic drugs n (%)	10 (28.5)	11 (26,5)	0,20
Creatinine (mmol / l)	126 (88-333)	131 (62-285)	0,61
Death n (%)	1 (3)	0 (0)	0,98

Table II: Characteristics of the two groups studied

The indications for radiological investigation with ICP injection are shown in Figure I and were primarily driven by coronary angiography, severe trauma (thorax, abdomen, pelvis), urological and digestive diseases.

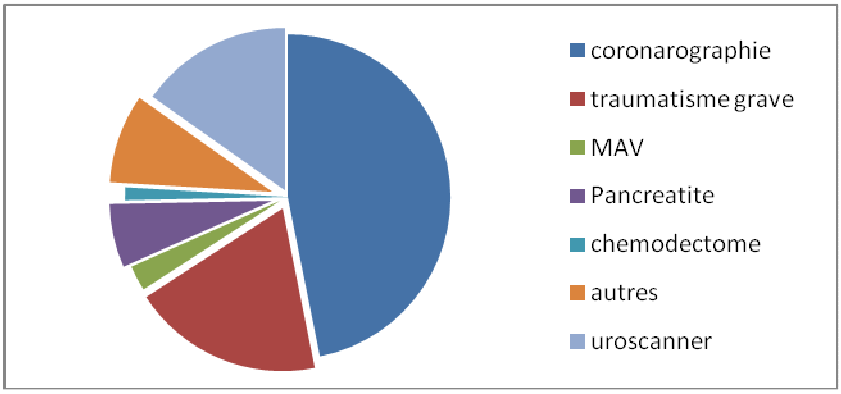

Figure 1: Procedures involving the injection of iodinated contrast.

The injection of the contrast agent was performed intraarterial 36 patients 54.5% (Figure 2).

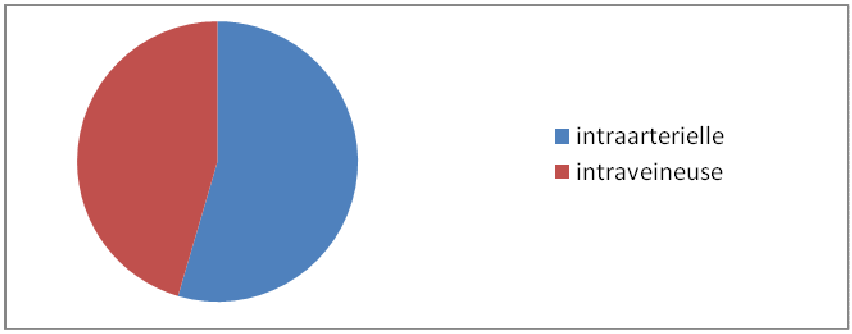

Figure 2: Distribution of PCI according to the route of administration

86 summers examinations made with an average of 1.2 ± 0.2 (p <0.17) by the patient (figure 3). The mean volume of PCI injected examination was 140 ± 35 ml, with a range from 60 to 275 ml.

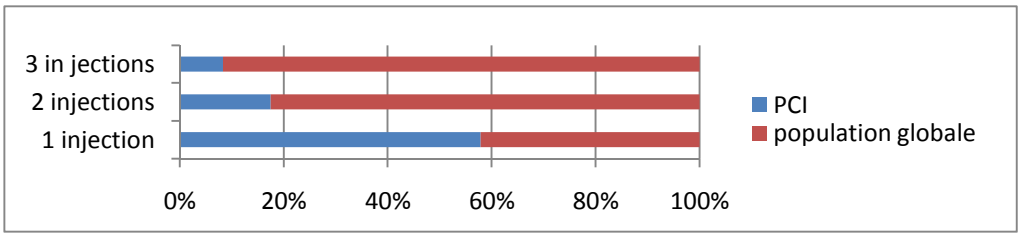

Figure 3: Number of examinations per patient with ICP injection

Administration of treatments renal toxicity has been reported in 21 patients, 10 of the group P1 and P2 group and 11 of vancomycin and amikacin represent over 70% of nephrotoxic drugs prescribed (Figure 4).

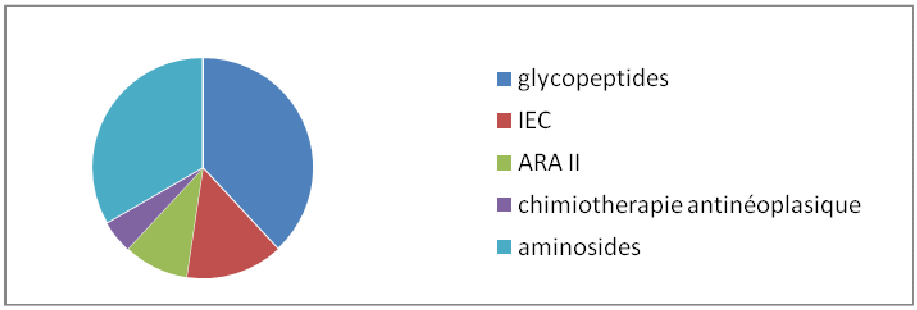

Figure 4: Distribution of nephrotoxic therapeutic

Regarding the incidence of contrast-induced nephropathy, 11 patients meet the AKIN definition IRA occurring after completion of a PCI injection examination with an average incidence of 16.7%, consistent with the literature data .

Changes in serum creatinine clearance and average over time are reported in Figure 5.

The use of renal replacement therapy was required in a patient or 3.12% for P1, P2 vs 0%. In this patient a hemodialysis session was necessary and performed SLED mode.

Hidden nephroprotective results show a higher effect of hydration protocol with urine alkalinization compared to a single rehydration.

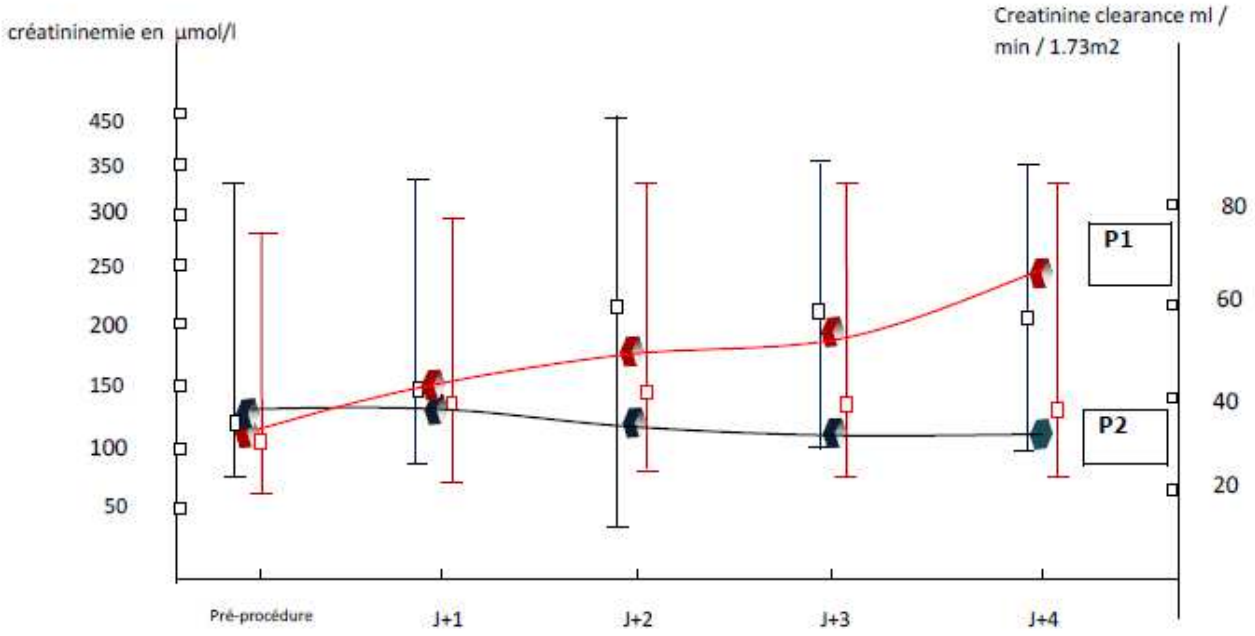

Figure 5: Values of minimum and average maximum of creatinine with curves of evolution of the average creatinine clearance in time depending on the group studied.

In multivariate analyzes certain factors are independent predictors of the occurrence of IRA induced by PCI were identified, there is a creatinine clearance <60ml / min / 1.73 m2 (OR = 1.07 p <0.08), intra-arterial injection of PCI (OR = 1.07, p <0.15), a quantity of PCI> 120 ml (OR = 1.62 p <0.15) and the IGS II> 30, OR = 1.07 p <0.08)

Discussion:

The NPC is defined by a serum creatinine increase of 44.2 mmol / l (or 0.5 mg / dl) or a relative increase of 25% from the base of a given patient serum creatinine (AKIN definition group)

occurring 48 to 72 hours after an injection of PCI [3]. It is a common and serious condition in the patient resuscitation, especially since these patients have hemodynamic instability (hemorrhagic shock or septic shock), they are under nephrotoxic therapy (antibiotics, diuretics ...). The incidence of NPC is extremely variable from 2 to 50%, while it k remains between 0.6 to 2.3% in medical services [4].

In the ICU, several risk factors are often associated in the same patient explaining the greater frequency of these NPC in [5]. The overall severity of patients evaluated by the score of organ failure, Sequential Organ Failure Assessment (SOFA, excluding his "kidney" component) was associated with a greater increase in serum creatinine after injection of PCI. [6] A more comprehensive assessment of the specific risk factors resuscitation would allow better comparison of the incidence of study of the NPC and the construction of predictive risk scores NPC, as has been done for other categories of patients [7] .

The NPC stems mainly from two phenomena. Medullary hypoxia-induced vasoconstriction secondary to impaired metabolism of vasoactive factors (endothelin and nitrogen monoxide). The hyper-osmolality induced hyperviscosity PC, with its rheological consequences resulting in a spinal cord hypoperfusion.

PCI are small molecules of low molecular weight which enables them to cross the vascular endothelium. They are classified based on three physicochemical characteristics: Their iodine content (which directly affects their radiopacity), their high osmolality, bass, or iso-osmolar and viscosity (Table 3) .They remain a modifiable risk factor and identification of the highest risk allows to take preventive measures of NPC. Thus, the radiological investigation should be done with the lowest volume, with product iso or hypo-osmolar and spacing of at least 48 hours (ideally 5 days) of two imaging studies with PCI injection [8].

Table 3: Properties of iodinated contrast agents commonly used

DCI (trade name)	Iode (mg/ml)	Osmolalité (WOSM / kg)	Viscosity at 37 ° C (mPa.s)
High osmolality: ionic monomer			
Ioxitalamate meglumine (Telebrix®)	300 ; 350	1 710	5,3
Low osmolality: nonionic monomer			
Iopamidol (Iopamiron®)	200 ; 300 ; 370	413 ; 616 ; 796	2,2 ; 4,7 ; 9,4
Iohexol (Omnipaque®)	180 ; 240 ; 300 ; 350	360 ; 510 ; 640 ; 780	2 ; 3,3 ; 6,1 ; 10,6
Ioméprol (Ioméron®)	150 ; 200 ; 250 ; 300 ;	301 ; 362 ; 435 ; 521 ; 618 ; 726	1,4 ; 2 ; 2,9 ; 4,5 ;
Iobitridol (Xenetix®)	350 ; 400	585 ; 695 ; 915	7,5 ; 12,6
Iopromide (Ultravist®)	250 ; 300 ; 350	607 ; 774	4 ; 6 ; 10
	300 ; 370		4,6 ; 9,5
Iso-osmolar: nonionic dimer			
Iodixanol (Visipaque®)	270 ; 320	290	5,8 ; 11,4

The diagnosis of NPC based on the finding of an IRA acknowledged before the rise of creatinine and decreased urine output.

In a critical care setting, quantification of diuresis in the first six hours of admission increases the ARI detection sensitivity [2]. Diuresis totalized to six hours is as effective as hourly diuresis to predict the occurrence of IRA. [9]

The NPC are many risk factors are linked to some other patient are related to the review.The main risk factor is the patient prior impaired renal function. The risk of NPC becomes significant from the GFR 45 mL / min / 1.73 m2. Hypovolemia and dehydration, easily modifiable risk factors in the ICU were evaluated by numerous studies that have demonstrated the beneficial effect of hydration protocols [10] and the deleterious effect of diuretics.

Comorbidities such as diabetes, hypertension and anemia also are recognized risk factors. Finally, the risk is increased by nephrotoxic treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, diuretics in high doses cove acyclovir. Their disruption is not always possible leading up to monitor the benefit / risk of the exam with ICP injection, and decide on its cancellation or its postponement to minimize renal hypoperfusion during the examination. [11]

In the examination-related risk factors, intra-arterial administration of a PC seems more toxic than intravenous administration because of a more direct renal exposure and risk superimposed cholesterol emboli. The total volume, osmolality and type of the PC are also recognized risk factors. PC hypoosmolar (osmolality of 500 to 800 mosmol / kg) are associated with a lower incidence of NPC compared to hyperosmolar PC (1400 to 1800 mosmol / kg).

The study by Nyman et al shows that a ratio (g iodine / GFR) <1 was associated with NPC risk of only 3%, compared to an NPC risk by 25% in case report (g iodine / DFG)> 1 [12].

It is therefore essential to recognize patients at risk of developing NPC in order to develop a prevention strategy. For hospitalized patients, having made a creatinine available, the clinical score Mehran has been validated to quantify the risk of NPC (Table 3). [7]

Table 4: Mehran Score PCI to quantify the risk of nephropathy

Risk factors	**Score**
hypotension	5
Against aortic pulse	5
Heart failure (NYHA III or IV, previous PAO)	5
Age> 75 years	4
Anemia (man Hb <90g / l, wife Hb <80 g / l)	3
diabetes	3
Volume of contrast medium	1 per 100 ml
DFG (ml/min/1,73m^2) selon créatininémie : - DFGe < 60 - DFGe 40-50 - DFGe < 20	 2 4 6

Score total	**Risk of increased creatinine of 44 mmol / l or> 25%**	**Dialysis Risk**
<5	7,5%	0,04%
6A10	14%	0,12%
11-15	26,1%	1,09%
> 16	57,3%	12,6%

DFGe: estimated glomerular filtration rate according to the formula of MDRD (Modification of diet in renal disease).
OAP: acute pulmonary edema

Several PCI nephropathy Prevention strategies have been proposed.It is accepted that an adequate hydration can limit the occurrence of NIPC. It is performed with a sodium chloride solution (0.45% or 0.9% rather [10] at a rate of 1 ml / kg per hour) over 24 hours framing PCI injection.

The preventive effect of sodium bicarbonate has been demonstrated in a randomized using isotonic sodium bicarbonate 1.4%, administered one hour before the administration of PC due to a bolus of 3 ml / kg / hour, then an infusion of 1 ml / kg / hour for six hours after the PC [13]. Beyond volume expansion, urine alkalinization may explain this protective effect by reducing oxidative mechanisms in renal medulla.

In the context of the emergency or intensive care, is the minimum required to correct a preexisting hypovolemia before the injection of PCI, possibly with the aid of sodium bicarbonate while taking into account the potential adverse effects (acute pulmonary edema, hypercapnia).

Nevertheless, we can assume that blood volume resuscitation patient is often already optimized before considering the injection of PCI, often different situation cardiology patient, often treated with diuretics and fasting.

In the end, KDIGO recommendations (Kidney Disease: Improving Global Outcomes) of Acute Kidney Injury Work Group group have left the practitioner the choice between these two options open. [14]

On a practical level, it is always useful to stress the need for correction of reversible factors (anemia, hypovolemia, heart failure, eviction of nephrotoxic drugs ...). The volume expansion should start at least one hour before and end no earlier than three to six hours after the injection of the PC. The speed and degree of volume expansion should be tailored to the patient's clinical status (age, heart failure, blood volume).

Although PCI are dialysable, a one-time hemodialysis immediately after the PC injection showed no efficacy in the prevention of NPC in a randomized study [15].

CONCLUSION

The incidence of NPC increases due to a broad indication of interventional radiology gestures in a therapeutic as well as diagnostic in patients with comorbidities such as diabetes, chronic renal failure or effective hypovolemia. Preventive measures are essential. The circulatory optimization, using PCI iso or hypo-osmolar, limited amounts of PCI used and stopping other nephrotoxic agents are necessary to enable renal protection. The proper role of PCI in the multifactorial renal aggression critically ill patient seems low, but probably enough to influence the prognosis of patients.

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