Sodium bicarbonate plus N-acetyl cysteine to prevent contrast-induced nephropathy in primary and rescue percutaneous coronary interventions

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Abstract

Background: Contrast induced nephropathy is a common coronary interventional complication, representing 10% of all in-hospital renal failure cases. Multiple therapeutic agents have been tried to reduce the incidence of CIN. **Methods:** This prospective study has enrolled 105 myocardial infarction patients who underwent either primary percutaneous coronary intervention or received a failed thrombolytic therapy that necessitated a rescue PCI. Those were classified into 3 groups, the first receiving sodium bicarbonate, n-acetyl cysteine with hydration and the second receiving acetyl cysteine with hydration, while the third group cases received saline hydration only. **Results:** In the 3 groups the CIN occurred in 6,7 and 8 cases respectively of 35 patients of each group, representing 17.1%, 20% and 22.9% respectively with p=0.836. **Conclusion:** it can be concluded that in STEMI patients treated with primary PCI, there is no difference between NAC and SB with saline hydration, NAC with saline hydration, and saline hydration only.

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Introduction

In patients presenting with ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) reduces ischemic complications and improves survival, when compared with pharmacologic reperfusion with fibrinolytic agents[1]. Patients undergoing primary PCI, however, are at high risk of contrast-induced nephropathy (CIN), a complication that has a serious impact on in-hospital outcome and may partially affect the overall benefit of primary PCI. Indeed, in-hospital mortality has been shown to be 20 times higher in patients who experience CIN after primary PCI as compared with those without this complication [2]. Contrast-induced nephropathy is defined as impairment of renal function occurring within 48 hours after administration of contrast medium. It's manifested by an increase in serum creatinine level of 0.5 mg/dl or by a relative increase of 25% over the baseline value [3]. From all the measures that were established to prevent the contrast-induced nephropathy, The beneficial effects of hydration are generally agreed on, hence the strong recommendation included in guidelines [4]. Whether the sodium bicarbonate (NaHCO3) was useful in the prevention of CIN was reviewed in many studies, which was driven mainly by the fact that NaHCO3 prevent the contrast-induced acute kidney injury (CIAKI) through shutting the medullary H^+ reabsorption. This thesis though was weaned by the fact that medullary NaHCO3 is predominantly reabsorbed by the proximal tubules, so the medullary NaHO3 will be low[5,6]. The generation of reactive oxygen species is a recognized pathophysiological mechanism of CIN. In this regard, N-acetylcysteine (NAC) and sodium bicarbonate (SB) have been proposed as potent antioxidant strategies in the field of nephroprotection. Volume supplementation with SB, which has previously been shown to reduce CIN in elective procedures, has not been adequately tested in primary or rescue PCI, especially in combination with high-dose NAC. The aim of this study was to compare the clinical efficacy of the combination of SB and high dose NAC in a prospectively-enrolled cohort of all-comers STEMI patients with an historical cohort of STEMI patients receiving saline hydration plus high-dose NAC.

Patient and methods

This study included 105 patients who underwent either primary PCI or received a failed thrombolytic therapy necessitating rescue PCI (from 2-2014 until 6-2015). They were investigated for baseline and 48 hours after PCI for creatinine, urea and creatinine clearance for

detection of contrast-induced nephropathy (CIN). All patients signed an informed consent and the study was approved by the local ethics committee. The Key inclusion criteria were: Patients who were presented within 12 hours from the onset of symptoms with a new, or presumed new ST segment elevation in 2 or more contiguous leads of at least 2mm in leads V2-V3 or 1mm in other leads or those with new LBBB. Key exclusion criteria were: > 12 hours from symptom onset, underwent either primary or rescue PCI. Key exclusion criteria: patients over 90 years of age, end stage renal disease on dialysis Need of urgent cardiac surgery as coronary revascularisation instead of urgent PCI, known allergy to iodinated contrast or NAC, and pregnancy or lactation. Patients were classified into 3 groups:

- Group A: patients received hydration with normal saline with sodium bicarbonate (SB) (3 mL/kg per hour for 1 hour before, followed by 1 mL/kg per hour for 6 hours after procedure), plus high dose N-Acetyl Cysteine (NAC) (600 mg orally twice a day for 2 days).
- Group B: patients received hydration with normal saline plus high dose N-Acetyl Cysteine (NAC) (600 mg orally twice a day for 2 days).
- Group C: Patients received hydration with normal saline only (1 ml/kg of 0.45 percent saline per hour for 6–12 hours before and after the contrast).

Methods: Full history taking; including age, sex, coronary risk factors (smoking, diabetes, hypertension, dyslipidemia and previous myocardial infarction or coronary angiography with or without intervention), and –also- renal impairment risk factors (diabetes, hypertension, previous dye exposure, nephrotoxic drug use and renal impairment history). Physical examination (including arterial blood pressure ABP, pulse rate, neck veins examination, chest examination, and cardiac examination). Resting 12 lead ECG, with special attention for detection of ST- segment elevation myocardial infarction (STEMI). Laboratory investigations: Admission serum creatinine and urea which was measured at the time of admission and 48 hours after the procedure in the CCU. An estimated glomerular filtration rate (eGFR) was calculated by cockcroft-Gault formula in first day prior to PCI and 48 hours after[7]. Coronary angiography and PCI (either primary or rescue); coronary angiography done according to standard protocol, with all patients receiving 300 mg chewable aspirin, and 600 mg clopidogrel, and 10000 IU UFH after coronary anatomy

defined. Primary or rescue PCI was performed, including balloon angioplasty and/or stent implantation were performed only for infarction related artery (IRA) according to lesion anatomy, with successful mechanical restoration of antegrade flow and achieving the desired end results. Non-ionic, low-osmolality contrast agent (Iopromide) was used and volume of contrast medium used in every procedure was reported, While PCI complications were also reported. CCU phase, where all patients were admitted for conventional anti-ischemic therapy, with follow up, management according to patient group, and reporting complications. Finally, follow up; with special care to CIN detection, 48 hours creatinine, 48 hours urea, and 48 hours creatinine clearance.

End Point: The composite of in-hospital death, Major adverse cardiac events (MACE), need for dialysis and CIN. CIN was defined as a relative increase of ≥25% in serum creatinine concentration over the baseline value at 48 hours after PCI. Dialysis should be undertaken in patients with oligoanuria (urine output <20 ml/h for 24 h) despite the administration of more than 1 g intravenous furosemide and presence of volume overload.

Statistical analysis Data are presented as mean±SD for continuous data and as number (%) for categorical data. Between groups analysis was done using student t-test for continuous data and Chi-square test (or Fischer exact test) for qualitative data. Level of evidence was detected to be significant at P value<0.05. Data were collected and analyzed by SPSS (version 17, USA, IL).

Results: Baseline clinical characteristics of the study population

Table 1 shows the characteristics of the study population, which is consisted of 105 patients, of those there were 34 female patient, consisting 32% versus 68%, 71 male patients. The mean age was 62.23±8.42 years. There were a total of 56 diabetic patients (53.3%), and 57 hypertensive patients consisting 54.3% of cases. Also there were 25 dyslipidemic patients (23.8%) and 37 smokers (35.2%). Previous MI was found in a total of 44 patients (41.9%), and previous coronary angiography with or without intervention in 36 patients (34.3%).

Of the study population, 20 cases (19%) had renal impairment, while there were 17 patients who were on nephrotoxic drug or who were exposed to dye previously (16.2%).

Table 1: Characteristics of general study population	
	All (n=105 patients)
Age (mean± SD, in years)	62.23±8.42
Sex (females)	34 (32%)
DM	56 (53.3%)
HTN	57 (54.3%)
Dyslipidemia	25 (23.8%)
Smoking	37 (35.2%)
Previous MI	44 (41.9%)
Previous CA+/- PCI	36 (34.3%)
Renal impairment	20 (19%)
Nephrotoxic drug / dye exposure	17 (16.2%)

* CA: coronary angiography, DM: diabetes mellitus, HTN: hypertension, MI: myocardial infarction, PCI: percutaneous coronary intervention.

The clinical characteristics of the study groups are shown in Table 2. The comparison between the study groups does show that there were no statistically significant differences between the groups. The mean age in group A was 61.2±8.512 versus 64.34±8.504 in group B, while in group C the mean age was found to be 61.06±8.04 (p= 0.167). There were 13 female patients in group A representing 37.1% of group A cases verses 10 in group B (28.6%), while in group C there were 11 ones (32.4%), (p= 0.738). Diabetes mellitus was found in 19 patients

(54.3%) of group A patients while it was in 21 patients (60%) of group B cases versus 16 patients (45.7%) of group C cases (p value 0.483).

Hypertension was present in 21 patients (60%) of group A versus 19 patients (54.3%) of group B cases and 17 patients (48.6%) of group C cases (p = 0.631). There were 10 dyslipidemic patients in group A (28.6%) versus 9 in group B (25.7%), and 6 cases in group C (17.1%), (p = 0.505). Smokers were distributed as most in group A with 16 smokers (45.7%) versus 9 smokers in group B (25.7%), and 12 smokers in group C (34.3%), (p= 0.214).

There were previous myocardial infarction in 14 of group A cases representing 40% of the group cases, this versus 16 of group B (45.7%), and 14 cases too –as in group A- within group C cases (40%), (p= 0.855). The previous coronary angiography –being that with or without intervention- between the study groups was present in 12 patients in each of the study groups that represented 34.3%, (p= 1.000). Renal impairment was there in 8 cases of group A (22.9%), while groups B & C was equal with 6 patients each (17.1%), (p= 0.781). Lastly, there were 7 patients in each group of A & B with nephrotoxic drug use or previous dye exposure that represented 20%, while in group C there were only 3 patients that represents 8.6% (p= 0.325).

Clinical presentation:

The clinical presentation of the study groups is shown in Table 3.

Chest pain was the leading clinical presentation, which was there in 102 cases of the study population, those came as all of group A cases, and all but 2 of group B – 33 patients, (94.3%), and all but one of group C cases – 34 patients (97.1%), (p= 0.357). Clinical heart failure was found in equal numbers between the study groups with 5 patients in each group (14.3%), (p= 1.000). Palpitation was present in 8 of group A cases (22.9%) versus 12 patients in group B (34.3%), and 7 in group C (20%), (p= 0.351).

The arterial blood pressure (ABP) values between the group studies had no statistical differences (p= 0.283). Of note the pulse rate was statistically significant between the study groups with group A with a mean pulse rate of 95.89±11.261 beat per minute (bpm), while group B had a mean pulse rate of 98.17±11.615 bpm, and group C showed a mean pulse rate of 89.94±11.827 with a p value of 0.011.

Figure 1, shows the distribution of the myocardial infarctions between the study population which was follows:

- Anterior MI: 18 patients (17.1%).
- Inferior MI: 19 patients (18.1%).
- Lateral MI: 20 patients (19%).
- Antero-lateral MI: 14 patients (13.3%).
- Infero-lateral MI: 15 patients (14.2%).
- Antero-septal MI: 20 patients (19%).

Table 2: Clinical characteristics of study groups

	Group A (n=35)	Group B (n=35)	Group C (n=35)	P value
Age (mean± SD, in years)	61.2±8.512	64.34±8.504	61.06±8.04	0.167
Sex (females)	13 (37.1%)	10 (28.6%)	11 (32.4%)	0.738
DM	19 (54.3%)	21 (60%)	16 (45.7%)	0.483
HTN	21 (60%)	19 (54.3%)	17 (48.6%)	0.631
Dyslipidemia	10 (28.6%)	9 (25.7%)	6 (17.1%)	0.505
Smoking	16 (45.7%)	9 (25.7%)	12 (34.3%)	0.214
Previous MI	14 (40%)	16 (45.7%)	14 (40%)	0.855
Previous CA+/- PCI	12 (34.3%)	12 (34.3%)	12 (34.3%)	1.000
Renal impairment	8 (22.9%)	6 (17.1%)	6 (17.1%)	0.781
Nephrotoxic drug/dye exposure	7 (20%)	7 (20%)	3 (8.6%)	0.325

** CA: coronary angiography, DM: diabetes mellitus, HTN: hypertension, MI: myocardial infarction, PCI: percutaneous coronary intervention, SD: standard deviation.

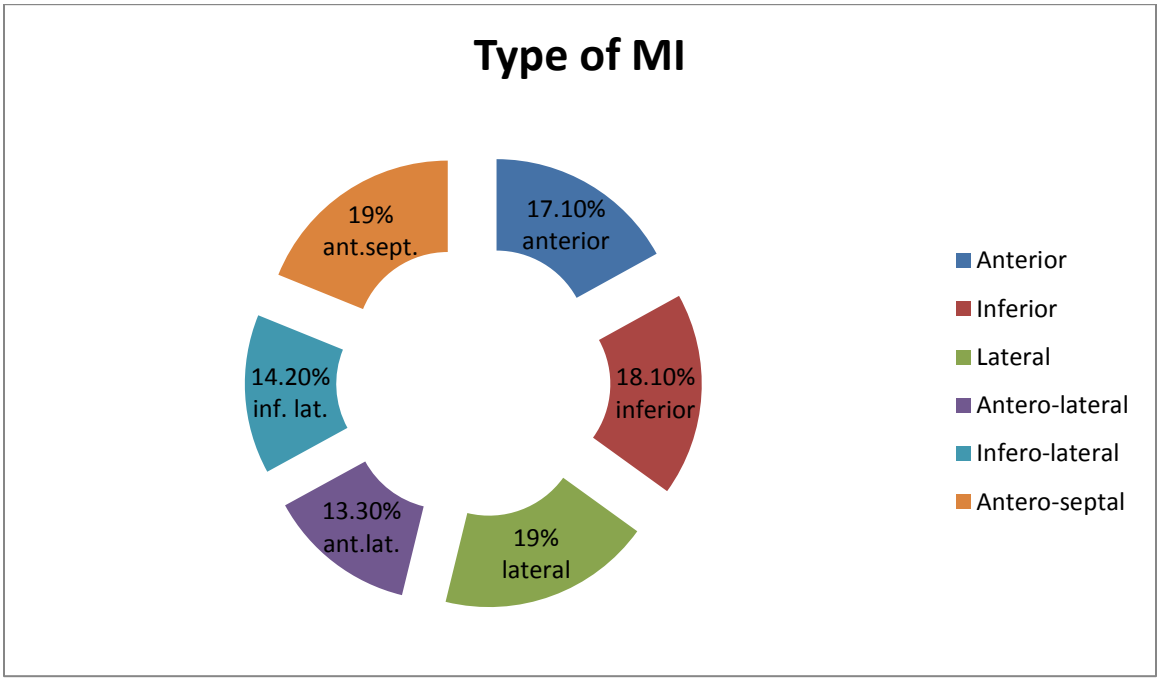

Figure 1: distribution of types of myocardial infarctions in study population.

Table 3: Clinical presentation in study groups

	Group A (n=35)	Group B (n=35)	Group C (n=35)	P Value
Chest pain	35 (100%)	33 (94.3%)	34 (97.1%)	0.357
Clinical HF	5 (14.3%)	5 (14.3%)	5 (14.3%)	1.000
Palpitation	8 (22.9%)	12 (34.4%)	7 (20%)	0.351
ABP (mmHg)	138.57±18.848 /88.57±12.282	136.43±25.222 /89.29±16.678	130.00±25.350 /85.43±16.994	0.283
Pulse rate (bpm)	95.89±11.261	98.17±11.615	89.94±11.827	0.011
Anterior MI	5 (14.3%)	6 (17.1%)	7 (20%)	0.818

Inferior MI	7 (20%)	5 (14.3%)	7 (20%)	0.773
Lateral MI	7 (20%)	8 (22.9%)	5 (14.3%)	0.649
Antero-lateral MI	5 (14.3%)	4 (11.4%)	5 (14.3%)	0.921
Infero-lateral MI	5 (14.3%)	5 (14.3%)	5 (14.3%)	1.000
Antero-septal MI	6 (17.1%)	7 (20%)	7 (20%)	0.940

* ABP: arterial blood pressure, bpm: beat per minute, HF: heart failure, MI: myocardial infarction.

Baseline renal functions:

The baseline renal function is shown in Table 4, and Figure 2. There were no statistically significant differences between the study groups regarding the baseline creatinine level (p= 0.259), nor baseline urea nor baseline creatinine clearance values (p= 0.074 and 0.196 respectively).

Table 4: Baseline renal functions

	Group A (n=35)	Group B (n=35)	Group C (n=35)	P value
Baseline creatinine	1.25±0.375	1.211±0.404	1.111±0.308	0.259
Baseline urea	42.71±16.025	40.03±11.518	35.71±10.069	0.074
Baseline CrCl.	71.06±16.650	70.31±11.985	75.69±10.789	0.196

*CrCl.: creatinine clearance.

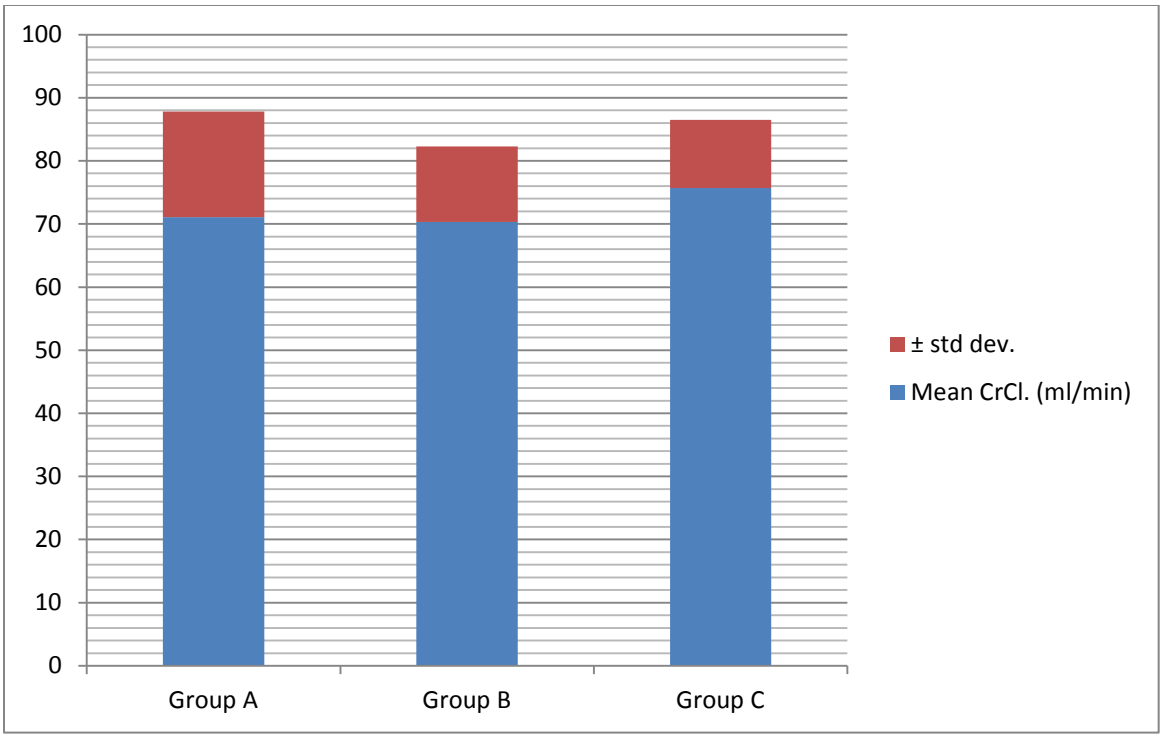

Figure 2: Baseline creatinine clearance between study groups. (p=0.196)

Procedural data:

The procedural data shown in Table 5 and Figure 3 shows that there were no statistically significant difference regarding the percutaneous coronary intervention (PCI) time which was found to be 36.0±5.374 minutes in group A versus 38.66±4.703 minutes in group B, and 37.43±4.931 minutes in group C (p= 0.090), while there was a statistically significant difference regarding the amount of the used dye. In group A mean 284.29±49.428 ml was used while in group B 316.00±40.161 ml was used, versus 301.71±52.496 ml for group C (p= 0.024).

Table 5: Procedural data

	Group A (n=35)	Group B (n=35)	Group C (n=35)	p value
PCI time (mins.)	36.0±5.374	38.66±4.703	37.43±4.93	0.090
Dye amount (ml)	284.29±49.428	316.00±40.161	301.71±52.496	0.024

*mins.: minutes, PCI: percutaneous coronary intervention.

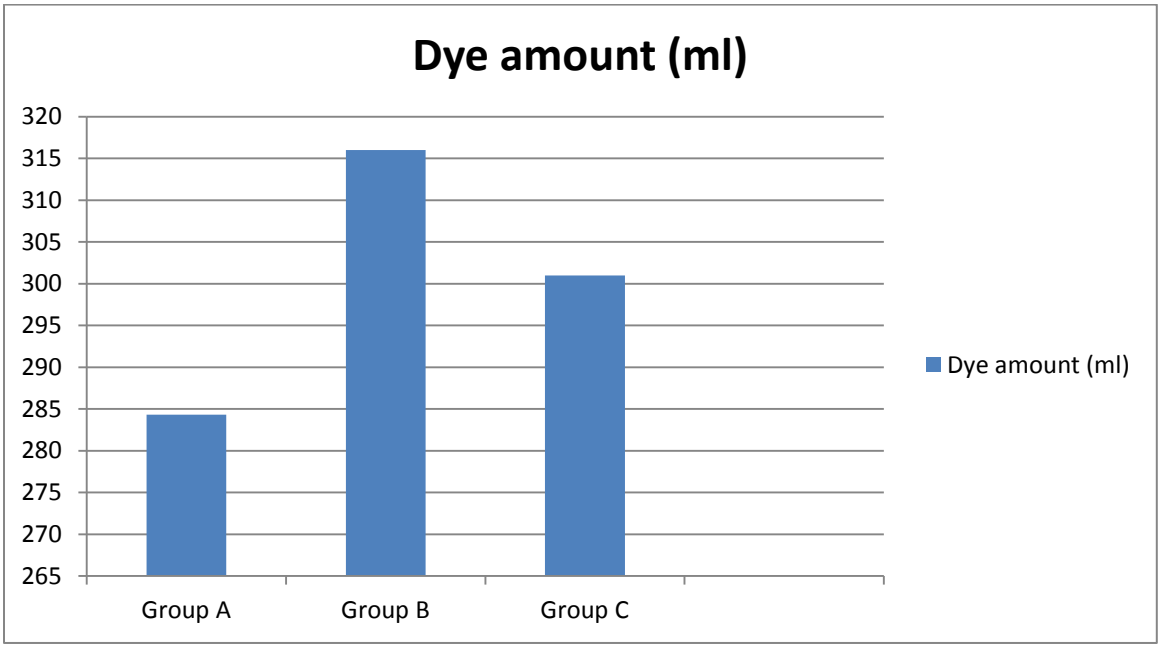

Figure 3: Dye amount between study groups. (p= 0.024).

Peri-procedural complications:

Table 6 and figure 4 show the peri-procedural complications, this including the one for which the study was aimed at: the contrast induced nephropathy (CIN).

Those complications were distributed in the study population as follows:

- Flow limiting dissection: in 19 patients (18.1%).
- Stent thrombosis: in 10 patients (9.5%).
- Abrupt vessel closure: in 7 patients (6.7%).
- Perforation: in 13 patients (12.4%).

- No reflow: in 17 patients (16.2%).
- Major bleeding: None.
- Minor bleeding: in 9 patients (8.6%).
- Ventricular arrhythmia: in 10 patients (9.5%).
- Recurrent unstable ischemia: in 20 patients (19%).
- Non-fatal MI: in 8 patients (7.6%).
- Cardiogenic shock: in 1 patient (1%).
- Stroke: in 6 patients (5.7%).
- CIN: in 21 patients (20%).
- Death: None.

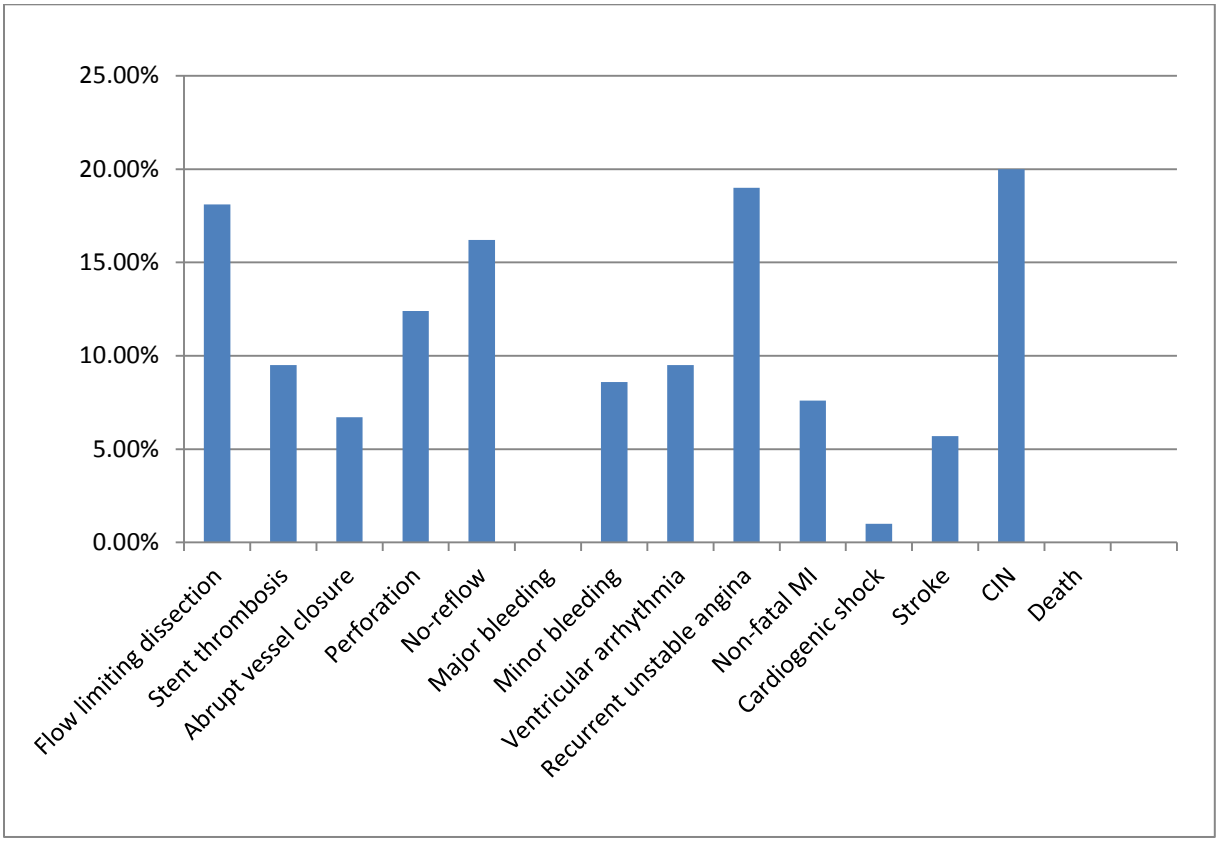

Figure 4: Peri-procedural complications in study population.

Flow limiting dissection did happen at most in group A with 8 patients suffering (22.9%) versus 4 in group B, and 7 in group C (11.4% & 20% respectively, (p= 0.434). All of those were treated with stenting. Stent thrombosis was observed in 2 patients of group A (5.7%), while it occurred most in group B with 5 patients suffered (14.3%), and in 3 of group C cases (8.6%), (p= 0.461). Abrupt vessel closure occurred in one case of group A (2.9%), while it happened in 3 cases of both groups B & C (8.6%) each, (p=0.542). Perforation was equal between groups A & C with 4 patients in each group (11.4%), while it complicated 5 of group B patients (14.3%), (p= 0.916). No-reflow occurred in 5 patients in both of groups A & B (14.3%), while it occurred in 7 of group C cases (20%), (p= 0.755). Major bleeding didn't complicate any of the study population, while minor bleeding complicated 3 of group A cases (8.6%), and 2 of group B (5.7%), versus 4 in group C (11.4%), (p= 0.694).

Ventricular arrhythmia did affect same numbers in groups A & C with 4 cases each (11.4%), 2 patients were affected in group B (5.7%). While recurrent unstable angina was found in 4 of group A cases (11.4%), versus 8 of each of groups B & C (22.9%), (p=0.372). Non-fatal myocardial infarction occurred in 1of group A cases (2.9%), versus 2 in group B (5.7%), while it occurred most in group C with 5 patients suffering (14.3%), (p= 0.172).

Stroke complicated 4 of group A cases (11.4%), while it didn't affect any of group B, and affected 2 of group C cases (5.7%), (p= 0.120). Cardiogenic shock didn't complicate any of groups A nor B, while it occurred to only one of group C cases (2.9%), (p= 0.364). And there were no mortality cases.

Regarding the contrast induced nephropathy (CIN) –which is the study aim- there were no statistically significant difference between the 3 of the study groups. The most of the CIN patients came in hydration only group, while least came in the ACC, SB plus hydration group. CIN did happen in a total of 21 cases of the study population (20%). Those were distributed as following:

- Group A had 6 CIN patients (17.1%).
- Group B had 7 CIN patients (20%).
- Group C had 8 CIN patients (22.9%).

With p=0.836. Figure 15 shows the CIN distribution between the three of the study groups.

Table 6: procedural complications				
	Group A (n=35)	Group B (n=35)	Group C (n=35)	p value
Flow limiting dissection	8 (22.9%)	4 (11.4%)	7 (20%)	0.434
Abrupt vessel closure	1 (2.9%)	3 (8.6%)	3 (8.6%)	0.542
Perforation	4 (11.4%)	5 (14.3%)	4 (11.4%)	0.916
No-reflow	5 (14.3%)	5 (14.3%)	7 (20%)	0.755
Major bleeding	0	0	0	1.000
Minor bleeding	3 (8.6%)	2 (5.7%)	4 (11.4%)	0.694
Ventricular arrhythmia	4 (11.4%)	2 (5.7%)	4 (11.4%)	0.643
Non-fatal MI	1 (2.9%)	2 (5.7%)	5 (14.3%)	0.172
Stroke	4 (11.4%)	0	2 (5.7%)	0.120
Cardiogenic shock	0	0	1 (2.9%)	0.364
CIN	6 (17.1%)	7 (20%)	8 (22.9%)	0.836
Death	0	0	0	1.000

*Unless mentioned else, all values are presented as number (%)
** MI: myocardial infarction, CIN: contrast induced nephropathy.

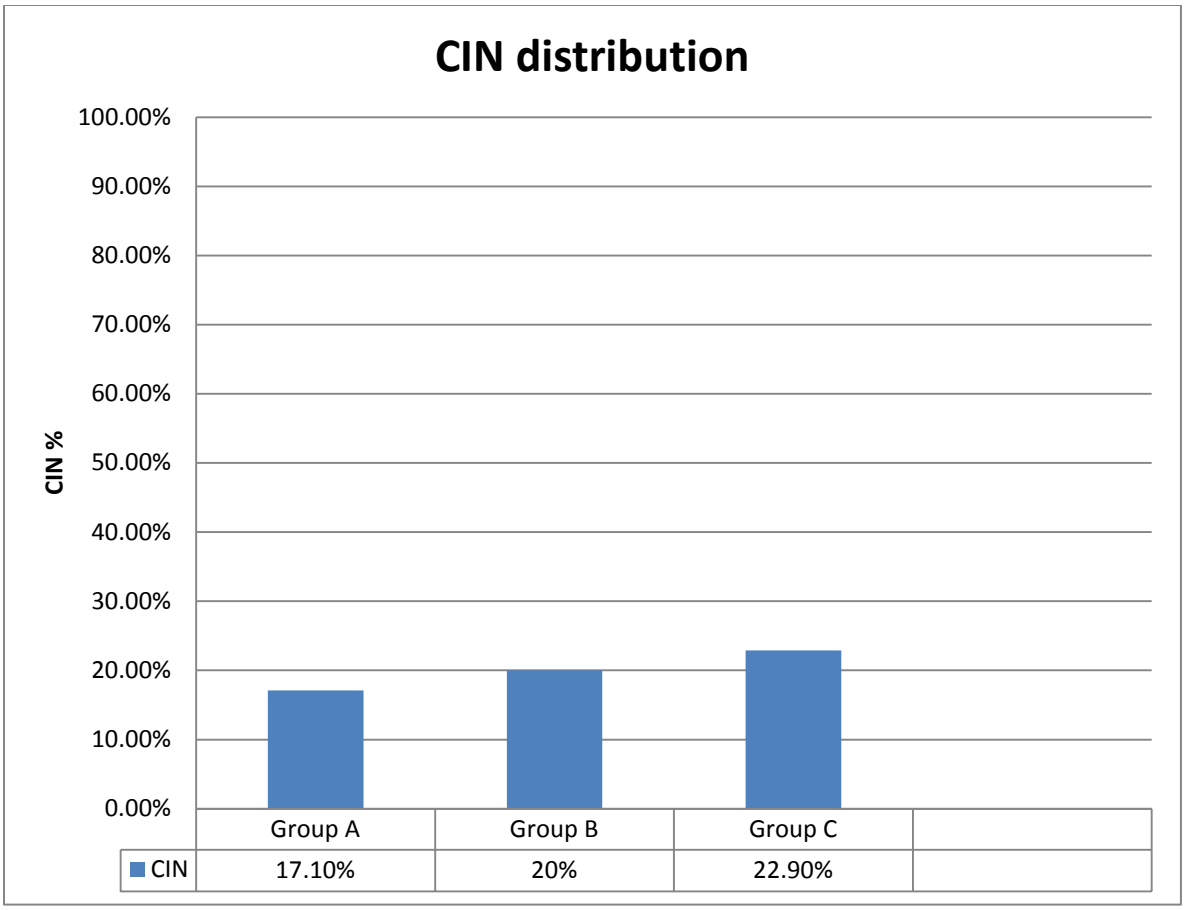

Figure 5: Contrast induced nephropathy (CIN) distribution between study groups. (p= 0.836).

Post procedural laboratory data of study groups:

Table 15 shows the post-procedural laboratory data regarding the 48 hours creatinine, urea and creatinine clearance levels.

The mean value of creatinine after 48 hours didn't show statistically significant difference between the study groups (p=0.656), nor the mean value of urea after 48 hours (p=0.093). Same with the mean 48 hours creatinine clearance value (p=0.142).

Table 7: post procedural data of study groups				
	Group A (n=35)	Group B (n=35)	Group C (n=35)	p value
48 hours creatinine	1.569±0.4807	1.549±0.6046	1.457±0.5282	0.656
48 hours urea	61.14±17.841	57.06±16.038	52.14±17.319	0.093
48 hours Cr.Cl.	56.80±15.654	58.89±12.184	63.14±12.596	0.142

DISCUSSION

In patients presenting with ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PPCI) reduces ischemic complications and improves survival, when compared with pharmacologic reperfusion with fibrinolytic agents. Increasing evidence exists that primary percutaneous coronary intervention (PCI) obtains rapid restoration of coronary artery patency and increases threatened myocardium salvage, thus preserving ventricular function and improving survival of patients with acute myocardial infarction (AMI) [1,8]. However, patients treated with primary PCI may represent a population at higher risk for CIN than those undergoing elective PCI. Several conditions may contribute to renal injury in this setting. Among them, hypotension or even shock, a large volume of contrast media, and the impossibility of starting a renal prophylactic therapy are the factors most likely involved. The impact of these factors on renal function, and the clinical relevance of CIN in the setting of primary PCI remain unknown [2]. The incidence of CIN in the current came in concordance to the incidence in other studies, occurring in 21 cases (20%) of our study population, those distributed as 6 in group A (17.1%), & in group B (20%), and 8 in group C (22.8%) [9,2]. Also the baseline serum creatinine levels and that after 48 hours levels was found to be in agreement with other studies [10,11,12]. Baseline creatinine level of the NAC plus SB with hydration group was 1.25 ± 0.375 mg/dl. in the current study, while in the NAC with hydration group it was 1.21 ± 0.40 mg/dl. Finally, in the hydration only group, the baseline creatinine

values were 1.11 ± 0.30 mg/dl. The 48 hours creatinine in our study were 1.56 ± 0.48 mg/dl. for the NAC, SB plus hydration group, in the NAC with hydration group, the 48 hours creatinine was 1.54 ± 0.60 mg/dl., Finally in the hydration only group, the 48 hours creatinine level of 1.45 ± 0.52 mg/dl., with p=0.259. The baseline creatinine clearance levels in the current study was 71.06±16.650 ml/min. for group A, and 70.31±11.985 ml/min. for group B, and 75.69±10.789 ml/min. for group C, with a p value of 0.196. While the 48 hours creatinine clearance levels were 56.80±15.654 ml/min., 58.89±12.184 ml/min. and 63.14±12.596 ml/min. for groups A, B and C respectively, with p=0.142. Those results –also- come in agreement with other relevant studies, albeit one of them used the 3 days post-procedure creatinine levels [10].

Based on the results of the current study, it can be concluded that in STEMI patients treated with primary PCI, there is no difference between NAC plus SB with saline hydration, NAC plus saline hydration, and saline hydration only.

Recommendations: Regarding this study we can recommend monitoring of high risk patients (old age, heart failure and renal insufficiency & diabetics) who underwent primary or rescue PCI for detection of CIN development, by daily serum creatinine level in the CCU. Also we can recommend that dehydration should be avoided; hydration has been proven to be safe, cheap, effective and rapid method that can be easily applied to all patients and during emergency (e.g. primary PCI). Therefore prophylaxis is crucial, especially in patients considered to be at high risk for CIN. And –after all- we recommend larger scale studies recruiting more patients.

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