Combination of hemoglobin and left ventricular ejection fraction as a new predictor of contrast induced nephropathy in patients with non-ST elevation myocardial infarction

Background: Hemoglobin concentration (Hb) and left ventricular ejection fraction (EF) are known predictors of contrast induced nephropathy (CIN). We hypothesized that combination of Hb concentration and left ventricular EF is superior to either variable alone in predicting contrast induced nephropathy in patients with acute coronary syndrome (ACS).

Material/Methods: Consecutive patients with ACS were prospectively enrolled. Patients considered for invasive strategy were included. Baseline creatinine levels were detected on admission and 24, 48 and 72 hours after coronary intervention. 25% or 0.5 umol/L increase in creatinine level was considered as CIN.

Results: 268 patients with ACS (mean age 58±11 years, 77% male) were enrolled. Contrast induced nephropathy was observed in 26 (9.7%) of patients. Baseline creatinine concentration, left ventricular EF, and Hemoglobin was significantly different between two groups. Contrast volume to estimated glomerular filtration rate ratio (OR: 1.310, 95% CI: 1.077–1.593, p=0.007) and the combination of Hb and left ventricular EF (OR: 0.996, 95% CI: 0.994–0.998, p=0.001) were found to be independent predictors for CIN. Hb × LVEF £ 690 had 85% sensitivity and 57% specificity to predict CIN (area under curve: 0.724, 95% CI: 0.625–0.824, p<0.001). In addition, Hb × LVEF £ 690 had a negative predictive value of 97% in our analysis.

Conclusions: The combination of Hb and left ventricular EF is better than either variable alone at predicting CIN in patients with ACS that undergone percutaneous coronary intervention. The prediction was independent of baseline renal function and volume of contrast agent.

Keywords: Contrast Induced Nephropathy • Anemia • Ejection Fraction • Non-ST Elevation Myocardial Infarction

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Background

Contrast-induced nephropathy (CIN) is a common cause of acute renal failure. As the usage of contrast agent increase at the diagnostic and interventional area, like coronary angiography (CAG), the frequency of CIN and the concern increase [1,2]. Although many risk factors have been identified, sometimes neither of them predict the development of CIN or in patients with no risk factors CIN could develop. The pathophysiology of the CIN remains incompletely understood [1,2]. It is thought that the contrast agent trigger the renal vasoconstricction and lead to renal tubular ischemia [3,4]. Also the contrast agent has a direct toxic effect to the renal tubular cells via reactive oxygen molecules [1–4]. After contrast agent administration, reach a peak level at 3–5 days and return to the baseline level after 1–3 weeks [8–11]. Contrast-induced nephropathy is the third leading cause of in-hospital acute renal failure [3,8]. Although, CIN consist 10–15% of the in-hospital acute renal failure and is seldom irreversible and require hemodialysis, it is associated with increassed in hospital stay, unfavorable in hospital and one year outcomes [8,9,12,13]. The incidence of CIN is varying widely, between 2–50%, in patients undergone a CAG [2]. As the risk factors increase the frequency of the renal failure increases dramatically [14].

The risk of the CIN increased in the presence of chronic renal failure, diabetes mellitus (DM), congestive heart failure (CHF), advanced age, anemia, female gender, dehydration and excess usage of contrast agent [4,15]. It is found that presence of anemia is a marker for renal function non-recovery in a group of heart transplanted patients with cardiorenal syndrome [16].

Identifying the risk factors play a corner stone for prevention of the CIN. As obviously seen, more information about risk factors should be clarified. Even though both anemia and decreased left ventricular ejection fraction (EF) per se are risk factors for CIN, as a new parameter for predicting the CIN, the combination of hemoglobin (Hb) and left ventricular EF (Hb×EF) could be superior to them. We investigate the predictive value of Hb×EF for CIN.

Material and Methods

Patient population

This was a prospective and observational study and conducted between February 2013 and July 2013. All consecutive patients admitted to the emergency clinic with chest pain and diagnosed as non-ST elevation acute myocardial infarction (NSTEMI) were included to the study if eligible. Patients on hemodialysis, with acute renal failure, cardiogenic shock, known allergy to contrast agent or taken contrast agent in 7 days, that were require immediate reperfusion treatment due to unstable hemodynamic profile and those refuse the study were excluded. After exclusion 268 (out of 310) patients were recruited to the study. All the patients were taken the written informed consent before enrollment and the local ethic committee of the hospital approve the study protocol.

Data collection

Patients' demographic, laboratory and clinical data were collected. The demographic data studied were age, sex, history of HT, DM, smoking and coronary artery disease (CAD). Baseline laboratory parameters were determined on admission and daily basis during the hospital stay. At the emergency clinic, all the patients were taken a standard 12-lead electrocardiogram (ECG). Left ventricular EF was measured after clinical stabilization, before CAG performed by using modified Simpson's method with a System V (Vingmed, GE, Horten, Norway) [17]. he cardiologists that perform the echocardiography were blind to the study.

Coronary angiography

After hospitalization all patients were given 300 mg aspirin (unless contraindicated), 300 mg clopidogrel and 0.1 mg/kg/day ×2 low molecular heparin (enoxaparin). According to the hemodynamic state, beta blocker and angiotensin converting enzyme inhibitor or angiotensin receptor blocker, 40 mg atorvastatin or 20 mg rosuvastatin were administered.

Coronary angiography was performed via femoral approach upon the written consent taken. Right and left coronary arteries, and if present, bypass grafts vessels were visualized. Intervention just to the culprit lesion was done at same session. A non-ionic iso-osmolar contrast agent was used in all cases. All procedures were performed at a high volume tertiary center (>3000 PCI/year) with expert clinicians blinded to the study.

Definitions

NSTEMI was defined as; patients with angina or symptoms of angina equivalent, with the increment of myocardial necrosis
biomarkers (troponin and/or creatine kinase-myocardial band (CK-MB)) and/or ischemic changes on ECG, like; ischemic T inversion or >0.5 mm ST segment depression on ≥2 consecutive leads. Diabetes mellitus and HT were defined if patients were on medication at hospital admission. Anemia was defined if hematocrit level <39% in men and <36% in women according to the World Health Organization [18].

Follow-up

The estimated glomerular filtration rate (eGFR) was determined with the admission sCr by using Cockcroft-Gault formula [19]. Following the CAG, sCr level was measured every 24 hours for 3 days after the indexed procedure. Peak sCr level was used for determination of CIN. Admission Hb level and measured left ventricular EF after stabilization was recorded and used for statistical analysis.

Statistical analysis

Parametric variables were reported as mean ±SD or median (with interquartile range) and categorical variables as percentages. Student t-test was used for parametric variable and Pearson’s χ² test for categorical variables analysis. In order to detect independent predictors of CIN binary logistic regression analysis were done. In univariate analysis, parameters that show statistical or borderline significance (p<0.1) were included in multivariate analysis. For detection the best predictive value of Hb×EF, ROC curve analysis was used. A two-sided p<0.05 was used for statistical significance. All statistical analysis were performed by using the SPSS version 15.0 for Windows (SPSS, Inc., Chicago, Illinois).

Results

A total of 268 eligible patients (mean age 58±11, 77% male) out of 310 admitted to the hospital diagnosed as NSTEMI-ACS was baseline. Demographic, clinical and laboratory data of all patients is demonstrated in Table 1. The age, gender and body mass index of groups were comparable. Also past history of HT, DM, smoking and CAD were not different between groups. Left ventricular EF and admission Hb level were significantly lower in CIN developed group (p=0.006 and p=0.001 respectively). Killip class on admission was similar between groups. The volume of contrast agent used was not statistically different (p=0.275). Although baseline sCr level was significantly differ among CIN developed and non-developed patients, eGFR was not significantly different (p=0.013 and p=0.255 respectively). All other baseline laboratory parameters were comparable between groups.

Table 2 shows the results of univariate and multivariate logistic regression analysis. In univariate regression analysis, high density lipoprotein level, left ventricular EF, left ventricular EF <50%, baseline creatinine, baseline creatinine ≥1.5 umol/L, Hb concentration, presence of anemia, eGFR <60 ml/min, contrast volume >300 ml, contrast volume/eGFR and Hb×EF were found to be correlated with CIN development. Out of these parameters, contrast volume/eGFR and Hb×EF were showed to be independent predictors of CIN development (OR: 1.310, 95% CI: 1.077–1.593; p=0.007 and OR: 0.996, 95% CI: 0.994–0.998; p=0.001 respectively). As Hb×EF value increases, the risk of development of CIN decreases.

The predictive value of Hb×EF is shown in Table 3. The positive predictive value of Hb×EF ≤690 is found to be 17.6% and the negative predictive value is 97.2%.

Discussion

In this study we have showed that, in patients with NSTEMI-ACS, the combination of Hb and left ventricular EF is better than either variable at predicting CIN. This prediction is independent of baseline renal function and volume of contrast agent being used.

Even though CIN is a rare cause of chronic renal failure and require hemodialysis, it causes prolonged hospitalization, increses in hospital and long term adverse events and end-up in increase health cost [9,12,13]. Predicting and identifying patients that will develop CIN is essential. For this purpose various risk factors have been identified, proposed and applied in clinical practice [2–4]. Besides the more known risk factors like chronic renal disease and DM; anemia and low left ventricular EF have been found to be associated with CIN development [3,4,20–23]. A group of studies have investigated risk factors of CIN in ACS patients found similar risk factors as in non-ACS patients [24–26]. Although it was thought that, NSTEMI-ACS patients may be at higher risk of CIN development than STEMI-ACS patients due to older age, more diabetic patients and multi-vessel disease, the development of CIN found to be similar in patients undergone percutaneous coronary intervention for both NSTEMI-ACS and STEMI-ACS [27].

Anemia and left ventricular EF <35% found to be independent risk factors for CIN development [21]. Also anemia and low left ventricular EF are independent risk factor for development of CIN in both deteriorated and normal renal function patients [22].
Low left ventricular EF is a risk factor both for CIN and persistent nephropathy [23]. In a group of patients that have moderate renal dysfunction, anemia found to be associated with higher incidence of CIN irrespective of baseline eGFR [28]. In a study

| Variables                        | All patients N=268 | Patients with CIN N=26 | Patients without CIN N=242 | P     |
|----------------------------------|--------------------|------------------------|-----------------------------|-------|
| Age – years                      | 58±11              | 60±11                  | 58±11                       | 0.543 |
| Sex – male (%)                   | 207 (77)           | 18 (69)                | 189 (78)                    | 0.305 |
| BMI – kg/m²                       | 28.4±4.6           | 27.3±3.9               | 28.5±4.7                    | 0.245 |
| History                           |                    |                        |                             |       |
| Hypertension (%)                  | 163 (61)           | 144 (60)               | 19 (73)                     | 0.178 |
| Diabetes (%)                      | 78 (29)            | 10 (39)                | 68 (28)                     | 0.275 |
| Smoking (%)                       | 116 (43)           | 11 (42)                | 105 (43)                    | 0.916 |
| Dyslipidemia (%)                  | 138 (52)           | 11 (42)                | 127 (53)                    | 0.314 |
| Previous CABG (%)                | 24 (9)             | 2 (8)                  | 22 (9)                      | 0.812 |
| Previous PCI (%)                  | 36 (13)            | 2 (8)                  | 34 (14)                     | 0.548 |
| Clinical                          |                    |                        |                             |       |
| Peak troponin I – ng/ml           | 2.66±5.17          | 3.73±7.47              | 2.51±4.87                   | 0.531 |
| Peak CKMB – IU/ml                 | 41±42              | 41±37                  | 42±43                       | 0.962 |
| LVEF – %                          | 52±10              | 47±10                  | 53±10                       | 0.006 |
| ST segment depression (%)         | 66 (25)            | 7 (27)                 | 59 (24)                     | 0.775 |
| Killip class >1 (%)               | 12 (5)             | 2 (8)                  | 10 (4)                      | 0.328 |
| Contrast volume – ml              | 173±75             | 190±91                 | 171±73                      | 0.275 |
| Ad-hoc PCI (%)                    | 82 (31)            | 9 (35)                 | 73 (30)                     | 0.649 |
| Laboratory                        |                    |                        |                             |       |
| Baseline creatinine – mg/dl       | 1.13±0.54          | 1.45±1.43              | 1.10±0.32                   | 0.013 |
| Baseline eGFR – ml/min/1.73 m²    | 87±35              | 81±45                  | 88±34                       | 0.255 |
| Glucose – mg/dl                   | 135±68             | 135±63                 | 136±68                      | 0.326 |
| Total cholesterol – mg/dl         | 189±50             | 187±60                 | 189±49                      | 0.842 |
| LDL cholesterol – mg/dl           | 114±38             | 110±44                 | 114±37                      | 0.607 |
| HDL cholesterol – mg/dl           | 40±10              | 45±11                  | 40±10                       | 0.026 |
| Triglyceride – mg/dl              | 186±135            | 161±105                | 188±139                     | 0.334 |
| Hemoglobin – g/dl                 | 13.1±2.0           | 12.0±2.3               | 13.2±1.9                    | 0.001 |
| White blood cell – 10³/ml         | 9.2±3.1            | 9.3±3.6                | 9.1±3.1                     | 0.455 |
| Platelets – 10³/ml                | 248±72             | 261±107                | 246±67                      | 0.510 |

Variables are reported as mean ± standard deviation or counts (percentages). CIN – contrast induced nephropathy; BMI – body mass index; CABG – coronary artery bypass graft; CK-MB – creatine kinase-myocardial band; PCI – percutaneous coronary intervention; eGFR – estimated glomerular filtration rate; LDL – low density lipoprotein; HDL – high-density lipoprotein; LVEF – left ventricular ejection fraction.

Table 1. Baseline characteristics of study population and comparison of patients with and without contrast induced nephropathy.
that examined additional risk factors and tried to determine a risk model in high risky patients (eGFR < 60 ml/min) found that, despite routine prophylaxis 11.4% patients developed CIN [29]. They propose a risk model including; age, contrast volume, post-PCI CK-MB level and eGFR. They found that as the score increase as well the incidence of CIN. There are also risk models developed, that contain left ventricular EF [30,31]. Among these risk scores, the most known and popular one is the Mehran risk score [32]. This risk score gives point to each parameters and categorized CIN into 4 groups. To remember

Table 2. Univariate and multivariate analysis of contrast induced nephropathy in patients with NSTE-ACS.

|                        | Univariate | Multivariate |
|------------------------|------------|--------------|
|                        | OR | 95% CI | p  | OR | 95% CI | p |
| Age                    | 1.011 | 0.976–1.048 | 0.541 |
| Age >75                | 1.260 | 0.280–5.677 | 0.763 |
| HT                     | 1.847 | 0.748–4.561 | 0.183 |
| DM                     | 1.590 | 0.688–3.677 | 0.278 |
| HDL                    | 1.040 | 1.004–1.077 | 0.030 |
| LVEF                   | 1.050 | 1.091–1.103 | 0.008 |
| LVEF <0.50             | 2.847 | 1.245–6.509 | 0.013 |
| Baseline creatinine    | 2.135 | 1.011–4.511 | 0.047 |
| Baseline creatinine >1.5 mg/dl | 2.643 | 0.900–7.761 | 0.077 |
| Hemoglobin concentration | 0.762 | 0.634–0.916 | 0.004 |
| Presence of anemia     | 3.419 | 1.496–7.814 | 0.004 |
| eGFR                   | 0.994 | 0.981–1.006 | 0.351 |
| eGFR < 60 ml/min/1.73 m² | 2.271 | 1.039–4.963 | 0.040 |
| Contrast volume        | 1.003 | 0.998–1.008 | 0.238 |
| Contrast volume >300 ml | 0.397 | 0.134–1.172 | 0.095 |
| Contrast volume/eGFR   | 1.367 | 1.110–1.683 | 0.003 | 7.3 | 1.310 | 1.077–1.593 | 0.007 |
| Hemoglobin × EF        | 0.996 | 0.993–0.998 | <0.001 | 10.8 | 0.996 | 0.994–0.998 | 0.001 |

OR – odds ratio; CI – confidence interval; HT – hypertension; DM – diabetes mellitus; HDL – high density lipoprotein; LVEF – left ventricular ejection fraction; eGFR – estimated glomerular filtration rate.

Table 3. Predictive value analysis of hemoglobin × left ventricular ejection fraction.

|                | CIN | No CIN |
|----------------|-----|--------|
| Hb × LVEF <690 | 22  (17.6) | 103 (82.9) |
| Hb × LVEF ≥690 | 4   (2.8)  | 139 (97.2) |

Sensitivity: 84.6%, specificity: 57.4%, positive predictive value: 17.6%, negative predictive value: 97.2%. CIN – contrast induced nephropathy; Hb – Hemoglobin; LVEF – left ventricular ejection fraction.

Figure 1. The receive-operating characteristic (ROC) curve of hemoglobin × left ventricular ejection fraction for predicting contrast induced nephropathy.

Hb × LVEF <690 had 85% sensitivity and 57% specificity to predict CIN. AUC – area under curve, CI – confidence interval.
and use these parameters and apply this risk score is not feasible. In this study we found and propose a more effective and feasible risk parameter in order to predict CIN. This parameter, Hb×EF ≤690, with 85% sensitivity and 57% specificity predict CIN and also it has a 97% negative predictive value. This parameter is easy to remember and could be applied at bedside in clinical practice. Another parameter found to be independently associated with CIN development is contrast volume/eGFR. By using this second parameter, after CAG imaging, more attention could be given to detected risky patients and appropriate medication could be preferred accordingly.

This study had some limitations. Firstly, this was a single center study and the study population was relatively small. The duration of hospitalization was not noted. The intra and inter-observer measurement of left ventricular EF was not evaluated.

Conclusions

In conclusion, it is easy and simple to measure left ventricular EF and evaluate Hb level. By using these 2 parameters a more definitive and predictive parameters for CIN could be obtained. Although chronic renal disease is the major risk factor for CIN, it will be very cost-effective to detect the patients under risk for CIN and take precautions in the presence of normal sCr level. By this way a more effective preventive treatment could be taken to the risky patient and reduce the hospitalization duration, in-hospital and long term clinical adverse outcomes.

Conflict of interest

None declared.

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