Does erythropoietin have a reno-protective impact in patients undergoing Coronary Artery Bypass Grafting? A randomized, double-blind, placebo-controlled trial

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Abstract: **Background**: Open heart surgery-related acute renal insult (OHS-RARI) is a typical inconvenience following cardiovascular surgery. Erythropoietin (EPO) has been appeared from many examinations to have a reno-defensive impact. **Objectives**: The present study was directed to explore the part of EPO in forestallingcoronary artery bypass graft surgery-related acute renal insult (CABG-RARI). **Patients and Methods**: Arandomized, double-blind, placebo-controlled trial was conducted prospectively on 70 male patients admitted to the Cardiothoracic Surgery Department, Qena University Hospital, candidate for elective on-pump CABG. They were divided into two groups; group I received 200 U/kg of rHuEPO (n = 35) intravenously (IV) three days preoperative and anotherdose of 100 U/kg IV at operation time. Group II received IV isotonic saline (NaCl 0.9%) (n = 35) intravenously three days preoperative and anotherdose at operation time. The serum creatinine (SCr), estimated glomerular filtration rate (eGFR) and urine neutrophil gelatinase-associated lipocalin (NGAL) were estimated to assess OHS-RARI. **Results**: The overall results of the present study revealed non-significant changes in the studied biomarkers concerning with assessment of the incidence of CABG-RARI and ARI between the two groups ($p>0.05$). **Conclusions**: Intravenous administration of 300 IU/kg of EPO did not protectagainst renaldamage in patients experiencing CABG.

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Keywords: Acute renal insult; CABG; Erythropoietin; Neutrophil gelatinase-associated lipocalin.

List of abbreviations

OHS-RARI: Open heart surgery-related acute renal insult; CABG-RARI: Coronary artery bypass graft surgery-related acute renal insult; EPO Erythropoietin; SCr: serum creatinine; GFR: glomerular filtration rate; eGFR: estimated glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin; CRD: chronic renal disease; CPB: cardiopulmonary bypass; CABG: coronary artery bypass graft; ACC: aortic cross-clamp; rHuEPO: recombinant human erythropoietin; RRT: renal replacement therapy; CBC: complete blood count; CABG: coronary artery bypass graft.

1. Introduction

Acute renal insult (ARI) was reported in about 5% of all hospital admissions. If it occurs in the pre- or postoperative period, it's associated with major complications, unsatisfactorily high mortality, morbidity and increase hospital stay with associated economic burden (1-4). It is well established that ARI that needs dialysis is very risky and can lead to high mortality (3-5), also, serum creatinine (SCr) impairment of level have been associated with a marked death rate (1, 2, 6-10). This risk of death is independent of other postoperative complications and co-morbidities (6-8).

Serum creatinine isn't a true marker of kidney injury, but it represents a functional change and it's affected by many factors, for example, age, ethnicity, sex, muscle mass, total body volume and drugs (11,12). The impairment in the glomerular filtration rate (GFR) more than 50% can occur earlier before it's detected in SCr (12-14). The capacity to identify ARI before it appears in SCr would represent a great progress in the treatment of ARI.

American Society of Nephrology adjusted a recognizable proof and characters of biomarkers for ARI as a key research zone. Several researches were done to identify the risk factors that lead to the occurrence of ARI. They found many factors and may be patient or technique related (3, 15, 16). Moreover, they noticed that post operative mortality frequently was seen with patient-related factors than technique associated factors. These risk factors lead to ARI via two mechanisms either insufficient renal perfusion or reduction of the renal reserve. However, not all of them are correctable prior to surgery. Age, hypertension, diabetes mellitus, heart failure, peripheral vascular disease, and chronic renal disease (CRD) were identified as patient-related factors (15,17,18). However, prior CRD is the most critical factor. As they found that

one-third of ARI cases needed dialysis was seen in patients with pre-existing CRD undergoing heart operations (7,17-19). OHS-RARI may occur due to prolonged cardiopulmonary bypass (CPB) time, combined valve and coronary artery bypass graft (CABG), and increased aortic cross-clamp (ACC) time during vascular surgery (19,20).

Accumulation of biomarkers in serum and urine occur during the incidence of ARI through different mechanisms during the process of kidney injury and repair. Also, the activated immune cells in the tubular lumen may produce biomarkers (NGAL, IL-18). Finally, the immune system and extra-renal tissues may secret biomarkers and the reduction in GFR will further augment this increase (21). Accordingly, it deserves to study the management options and laboratory investigations to anticipate or prevent OHS-RARI.

Erythropoietin (EPO) is a glycoprotein hormone member of the type 1 cytokine super family that is produced by the kidney type 1 fibroblasts (22),in response to insufficient tissue oxygenation (23). Via many mechanisms EPO can prevent ARI and help in kidney repair; prevention of apoptosis, augments new blood vessel formation, anti-inflammatory effect, and improves tissue regeneration.

Up to date, there are limited resources about the outcome of management options for ARI; however, therapeutic use of EPO seems promising for those “at risk” for ARI.

2. Patients and Methods

2.1 Study design

This prospective randomized double-blind, placebo-controlled trial was done at Cardiothoracic Surgery Department- Qena and Assiut University Hospitals-Egypt from July2014 to July 2016, after obtaining approval from the institutional ethics committee and written informed consent from all patients. The study included seventy patients aged 45-65years, scheduled for elective on-pump CABG. They were divided into group I (n=35): received IV 200 U/kg of recombinant human erythropoietin (rHuEPO) (5000 U, Recormon, Roche)3 days preoperatively, and 100 U/kg rHuEPO intraoperative; and group II (n=35): received 0.9% saline corresponding to the same time as in EPO group.

2.2. Exclusion criteria

a. ARI cases before the study.

b. CRD stage 5 or changes in SCr ≥ 50%, within 2 weeks prior to the study.

c. Drugs: nephrotoxic drugs and/or contrast media administration within two weeks preoperative.

d. Patients with a known allergy to rHuEPO.

e. Patients with valvular heart diseases, congenital heart diseases, congestive heart failure, cardiogenic shock or emergency operations were excluded.

The essential endpoint of this research might have been the frequency of CABG-RARI for the group I compared with group II. That definition from claiming CABG-RARI will be characterized as a ≥0. 3 mg/dl or alternately ≥ half increment in SCr levels from baseline inside the principal 48 hrs postoperative. Changes in SCr, eGFR and urine NGAL throughout the three postoperative days, postoperative complications, length of ICU and hospital stay, a requirement for RRT and all causes of hospital mortality were compared between both groups.

2.3. Perioperative management

The standard anesthetic care was done for all cases. Normocarbia was obtained by adjustment of the ventilator (tidal volume = 8 mL/kg, respiratory rate = 8 to14 breaths/min). Priming of CPB was established with a 1.6 L solution. All patients underwent the traditional on-pump CABG via standard median sternotomy. The institution of CPB via aortic cannula and single two-stage venous cannula in the right atrium. All cases were given warm antegrade blood cardioplegia via the aortic root cannula. Intraoperatively, the mean arterial pressure (MAP) was maintained at 50 to 80 mmHg and CPB flow at a rate of 2.0 to 2.4 L/min/m2. During the perioperative period, the fluid balance was maintained using Voluven® (Fresenius Kabi, Graz, Austria) and fresh frozen Plasma to maintain normovolemic status. Packed RBCs transfusion was done if the hematocrit <20% during CPB or <25% after CPB. Norepinephrine was used to establish a MAP between 65 to 90 mmHg postoperatively. Similarly, milrinone was used as an inotrope in right ventricular dysfunction and/or severe pulmonary hypertension cases. Diuretics were utilized the point when urine output under 0. 5 ml/kg/hr.

2.4. Laboratory workup

Complete blood count (CBC) with reticulocytic count was done three days as a baseline and 6 hrs preoperatively, and postoperative daily CBC for five days. SCr was estimated 12 hrs preoperative (baseline) and daily for five days post operatively in all cases. Real-time eGFR was calculated using the Cockroft-Gault formula.

Urine samples were taken12 hrs. preoperative (baseline) and 3,6,12, 18 and 24 hrspostoperatively. Samples were centrifuged at 2,000 g for 5 min and the supernatants stored at −70°C until assayed. Urinary NGAL concentration was measured using a commercial double-antibody sandwich ELISA kit (Glory Science, USA). Pre-ELISA, together optimal density concentration; that meets the respective NGAL protein concentration in the linear range of the standard curve; all urine samples were diluted. The inter-assay and intra-assay coefficients of variation for NGAL were < 5%. These assays were done duplicated and blinded.

2.5. Statistical analysis

The sample size was calculated with the use of a two-sided X2 test with a significance level of 0.05 and a power of 80%. Data were expressed as a mean ± SD for continuous variables and as percentages for discrete variables. Continuous data were analyzed by the Student's t-test for the equal variance or Mann–Whitney test for unequal variance and categorical valuables were investigated by the Pearson $\chi 2$ or Fisher's exact test. A two-sided p-value < 0.05 was considered significant. Two-way analysis of variance was utilized to compare continuous variables between both groups with Bonferroni post-hoc test for each time point. SPSS was used for statistical analysis (Version 15.0. for Windows; SPSS, Inc.) and significance was assigned when p values < 0.05.

3. Results

This study included 70 patients; they were randomly assigned into group I (rHuEPO group) and group II (placebo group). The patients' characteristics, preoperative and intraoperative data were postulated in Tables [1, 2]. Preoperatively, both groups were comparable as regard patients' characteristics, existing risk factors and medications. Moreover, there was no statistically significant difference between both groups as regard preoperative hemoglobin, hematocrit, reticulocyte count, SCr and eGFR. The operation time, ACC time, intraoperative fluid intake and urine output were equivalents between both groups.

Table 1. Patient characteristics and preoperative clinical data.

Variables	Group I N=35	Group II N=35	*P* value
Age (years): Mean ±SD	 50.7±5.2	 53.6±5.2	 0.146 (NS)[a]
Weight (kg): Mean ±SD Range	 69.1±8.0 60-85	 71.2±13.0 53-91	 0.2118 (NS)[a]
Hypertension N. (%)	23 (65.7%)	21 (60%)	0.621(NS)[b]
Diabetes Mellitus N. (%)	11 (31.4%)	15 (42.9%)	0.322 (NS)[b]
Preoperative medications: N. (%) ACEIs ARBs BBs CCBs Diuretics Statin	 15 (42.9%) 7 (20%) 19 (54.3%) 10 (28.6%) 12 (34.3%) 8 (22.9%)	 14 (40%) 6 (17.1%) 21 (60%) 11 (31.4%) 14 (40%) 12 (34.3%)	 0.808 (NS)[b] 0.759(NS)[b] 0.629 (NS)[b] 0.794 (NS)[b] 0.621(NS)[b] 0.290(NS)[b]
Hemoglobin (Mean ±SD, gm/dL)	12.13±0.54	12.13±0.67	0.482 (NS)[a]
SCr (Mean ±SD , mg/dL)	0.84±0.13	0.88±0.11	0.101 (NS)[a]
eGFR (Mean ±SD, mL/min/1.73 m2)	98.37±20.51	91.60±13.27	0.053(NS)[a]
Hematocrit (Mean ±SD, %)	36.17±2.63	36.32±2.16	0.3710 (NS)[a]
Reticulocyte count (Mean ±SD, %)	1.23±0.25	1.19±0.35	0.3066 (NS)[a]

a: Independent sample t-test, NS: non-significant (P >0.05); b: Pearson Chi-square test, ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BBs: beta blockers; CCBs: calcium channel blockers.; SCr: serum creatinine**; e**GFR: estimated glomerular filtration rate.

Table 2. Intraoperative data of the included patients.

Variables	Group I N=35	Group II N=35	*p* value
Operation time (Mean±SD, min.)	293.2±62.1	302.2±63.2	0.276(NS)[a]
CPB time (Mean±SD, min.)	104.3±14.4	101.3±16.5	0.215(NS)[a]
Intraoperative fluid balance			
Crystalloids (Mean±SD, ml)	1547.1±309.6	1530.9±306.2	0.413(NS)[a]
Colloids (Mean±SD, ml)	664.3±83.6	637.1±151.1	0.284(NS)[a]
Urine output (Mean±SD, ml)	1025.1±350.9	1001.7±281.4	0.380(NS)[a]
Patients transfused with packed RBCs N. (%)	24 (68.6%)	28 (80.0%)	0.274(NS)[b]
Packed RBCs transfused (Mean±SD, ml)	310.0±69.5	332.9±86.6	0.142(NS)[a]

Independent sample t-test, NS: non-significant (P >0.05); b: Pearson Chi-square test

A comparison of the SCr and eGFR between both groups; preoperative (baseline) and on the 1st, 2nd, 3rd, 4th and 5th day postoperatively; showed no statistically significant differences [Table 3]. Also, as regarding the all-time point's measurements of SCr and eGFR, there was a non-significant contrast (p >0.05) between both groups.

As regard NGAL concentrations in urine, both groups had a similar baseline concentration. However, within the first 24 hours; it was found higher than the baseline at all time points in both groups. But, without a noteworthy distinction in the mean urine NGAL concentrations between both groups [Table 4]. The reticulocyte count was comparable between both groups in the baseline. We reported a significant increase in the reticulocyte count percentage after administration of the first dose of rHuEPO in group I (1.23±0.25to1.50±0.28, p< 0.01). on the contrary, no significant changes reported group II (1.19±0.35 to 1.20±0.36) at the operation day. Furthermore, both groups were comparable as regards the baseline and postoperative hematocrit [Table 5]. The summary of the previously described results are shown in Figure-1.

In the present study, regarding CABG-RARI, it was noticed in 35.7% of cases. It occurred in 40% of cases in group II compared with 31.4% of cases in group I, however without a statistically significant difference between both groups (*p* >0.05). RRT was needed for one patient (2.9%) in each group. Both groups were comparable as regards mean ICU and hospital stay (group I were 2.9±1.01 & 15.1±3.43 days, while group II was3.2±0.9 & 14.8±2.65 days respectively) [Table 6].

Acknowledging other postoperative variables assessment in the present study such as Mechanical ventilation > 48hrs, Reintubation, Reoperation, there might have been no measurable contrast (p > 0.05) between both groups. In the hospital, one patient (2.9%) died in group I, while two patients (5.7%) in group II due to sepsis and acute respiratory distress syndrome. None of the patients formed unfriendly difficulties identified with EPO organization including thromboembolic occasions all around the study.

Table 3. Mean ±SD of serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) in both groups preoperatively (baseline), on the 1st, 2nd, 3rd, 4th and 5th day post-operative.

Variables	Group I N=35	Group II N=35	*p* value
SCr (Mean±SD, mg/dl):			
Baseline	84±0.13	0.88±0.11	0.101(NS)
1st day	0.93±0.19	1.01±0.24	0.064(NS)
2nd day	1.11±0.40	1.17±0.39	0.246(NS)
3rd day	1.11±0.79	1.19±0.57	0.315 (NS)
4th day	1.08±0.80	1.17±0.60	0.295 (NS)
5th day	1.08±0.82	1.13±0.60	0.389 (NS)
eGFR (Mean±SD, mL/min/1.73m2)			
Baseline	98.37±20.51	91.60±13.27	0.053 (NS)
1st day	91.43±25.14	83.43±18.86	0.077 (NS)
2nd day	81.11±37.60	76.20±22.71	0.255 (NS)
3rd day	91.40±37.55	78.29±29.46	0.054 (NS)
4th day	90.0±32.41	79.89±27.78	0.095 (NS)
5th day	92.86±35.22	83.14±30.01	0.109 (NS)

Independent sample t-test NS: non-significant (P- value >0.05)

Table 4. Mean ±SD of urine neutrophil gelatinase-associated lipocalin (NGAL) concentrations (ng/ml).

Studied groups	Urine NGAL (Mean ± SD, ng/ml)					
	Baseline	3 hrs	6 hrs	12 hrs	18 hrs	24 hrs
Group I N=35	64.06±24.39	160.66±24.79	218.63±82.64	165.80±58.42	136.03±60.13	120.34±51.58
Group II N=35	69.23±21.21	163.71±17.72	222.80±85.60	178.43±43.19	147.74±62.79	123.54±65.42
p-value	0.1736 (NS)	0.2773 (NS)	0.4177 (NS)	0.1537 (NS)	0.2141 (NS)	0.4105 (NS)

Independent sample t-test NS: Not significant (P > 0.05)

Table 5. changes of the reticulocytic count (%) and hematocrit (%) during the perioperative period.

Variables	Group I N=35	Group II N=35	*p* value
Reticulocytic count (%)			
• Baseline	1.23±0.25	1.19±0.35	0.307 (NS)
• Operative day (3 days after 1st dose)	1.50±0.28	1.20±0.36	0.0001***
Hematocrit (%)			
• Baseline	36.17±2.63	36.32±2.16	0.371 (NS)
• Day 0 preoperative	36.23±1.68	35.81±2.66	0.215 (NS)
• Day 0 postoperative	29.77±2.10	29.0±2.06	0.083 (NS)
• Day 1 postoperative	30.23±2.26	29.71±2.55	0.188 (NS)
• Day 2 postoperative	30.17±2.98	30.57±2.52	0.273 (NS)
• Day 3 postoperative	30.60±3.15	31.04±2.81	0.268 (NS)

Independent sample t-test NS: non-significant (P- value >0.05) *** *p*-value < 0.001

Table 6 Postoperative variables and outcomes of the included patients.

Variables	Group I N=35	Group II N=35	*p* value
Duration of ICU stay (Mean±SD, days)	2.9±1.01	3.2±0.9	0.162 (NS)[a]
Duration of hospital stay (Mean±SD, days)	15.1±3.43	14.8±2.65	0.351(NS)[a]
Acute kidney injury (AKI) N. (%)	11 (31.4%)	14 (40%)	0.454 (NS)[b]
Renal replacement therapy (RRT) N. (%)	1 (2.9%)	1 (2.9%)	1.00 (NS) [b]
Mechanical ventilation>48h N. (%)	2 (5.7%)	2 (5.7%)	1.00 (NS) [b]
Reintubation N. (%)	1 (2.9%)	1 (2.9%)	1.00 (NS) [b]
Reoperation N. (%)	1 (2.9%)	2 (5.7%)	0.555 (NS) [b]
Mortality N. (%)	1 (2.9%)	2 (5.7%)	0.555 (NS) [b]

a: Independent sample t-test, NS: non-significant (P >0.05); b: Pearson Chi-square test.

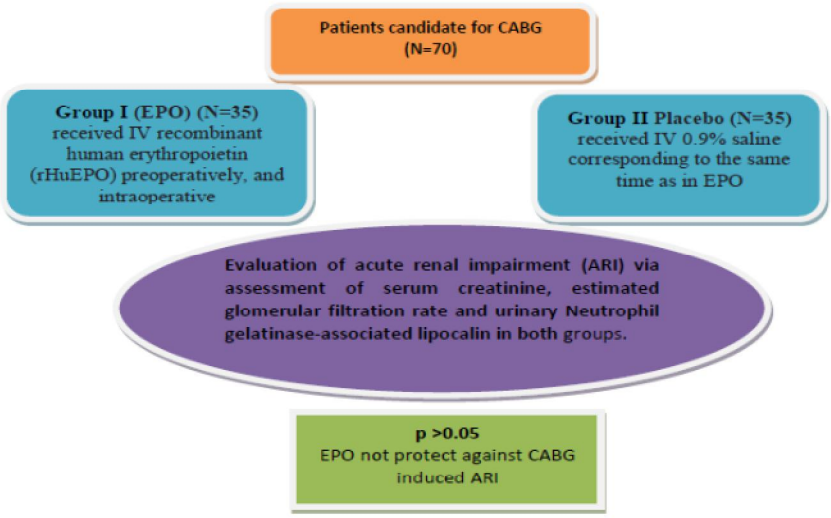

Figure 1. Summary of the overall results of the present study

4. Discussion

Provided for that vulnerability of the utilization of rHuEPO to save the kidney and the guaranteeing utilization of NGAL for identifying ARI, this study was done to assess the reno-protective impact of rHuEPO when started three days former of the onset from claiming cardiovascular surgery, furthermore during the operation. This early begin is exceptional likewise a method for protection against ARI over elective cardiovascular surgery patients. Those preferences for rHuEPO might have been assessed on the frequency of OHS-RARI, clinical results and changes in urine NGAL.

The baseline reticulocyte count was the same between the two groups. Interestingly, we noticed a significant increase in the reticulocyte count percentage after administration of the first dose of rHuEPO in group I, on the contrary, no significant changes reported group II on the operation day. Moreover, both groups were comparable as regards the baseline and postoperative hematocrit. As opposed to our results, two studies recently placed the reno-protective impacts of rHuEPO during cardiac surgery (24,25). However, in a study by Song et al (24), accounted a decrease in the frequency from claiming ARI from 29 to 8% within 5 days postoperatively; by administration of 300 U/ kg rHuEPO after induction of anesthesia. Tasanarong et al (25), evaluated those impact of a two-dose rHuEPO regimen, initial 200 U/kg 3 days before CABG and 100 U/kg afterwards anesthesia incitement and reported a statistically noteworthy contrastin eGFR 24, 48 and 72 hrs postoperatively in the EPO group and a decline over ARI from 38 to 14% in the EPO group. Likewise, they accounted statistically significant low urine NGAL levels in the EPO assembly postoperatively. So, these different effects might be expected on the selection of cases, sample size, time points of measurements, dose and/or timing of rHuEPO administration. Anyhow our outcomes are like Tasanaronget al (25) who found a change of the reticulocyte count three to four days following rHuEPO infusion. However, different investigations ahead cardiovascular surgery patients bring a neglected on the show this reno-protective impact (26-28).

In the EARLYARF trial (26), evaluated those reno-protective impact for rHuEPO in a double-blind controlled study of 162 general ICU patients with severe illness. They administered two doses of 500 U/kg rHuEPO. There were no differences accounted for SCr transforms between the two groups within one week from baseline. On the contrary to our study, rHuEPO was given throughout alternately after the ARI and over a heterogeneous critically sick assembly of patients that might differ starting with cardiovascular surgical cases.

In an alternate randomized controlled study, de Seigneux et al [27], evaluated different cardiac surgical patients. Postoperatively, 40,000 and 20,000 U of rHuEPO was given after ICU admission. They contrasted the levels of urine NGAL 48 hrs postoperatively to baseline. The contemplate didn't hint any reno-protective impact. However, it can be contended that late organization of rHuEPO might obstruct the reno-protective impacts of rHuEPO.

In a study by Kim et al (28), they administered 300 U/kg rHuEPO preoperatively in a high-risk heterogeneous cardiac surgical cohort, but generally with normal GFR. Erythropoietin was given for a comparable timing and dosing in a study by Song et al (24), the renal outcomes were measured by cystatin C and NGAL. Kim et al (28), might not show whatever renal protective impact about rHuEPO.

In a study conducted for cases with previous renal impairment undergoing CABG, by Dwadashi et al (29), they concluded that preoperative organization of 400 IU/kg of rHuEPO, had no reno-protective impacts. The third postoperative day for relative cystatin C level changes showed a non-statistically noteworthy distinction between the group compared to baseline. Moreover, the other kidney biomarkers or investigations (NGAL, SCr and eGFR) presented non-statistically significant differences among the groups. So, they reported no different contrasts in the end results between the groups.

In this prospective randomized controlled trial, we did not find any beneficial effect of pre-emptive rHuEPO administration on the prevention of ARI and the degree of renal injury in patients undergoing CABG. Four limitations were reported in this research. Firstly, the study was performed at a single center. Secondly, the results require more sample size for an adequate scope of the study. Thirdly, the author mentions the anti-oxidant impact of rHuEPO prophylaxis. So, future researches are needed to study it. Lastly, urinary NGAL was used as a biomarker for kidney function assessment, but other markers should be measured to precisely find any relevant differences.

In conclusion, the pre-operative IV administration of 300 IU/kg of EPO did not protect against renal damage in patients experiencing CABG. Also, it is failed to attenuate the increase in the urinary NGAL and improve the clinical outcomes. Further investigations are required will affirm that convenience from this regimen. Moreover, large studies are necessary on a survey for long-term results. A total assortment of claiming markers to renal capacity ought to make measured with faultlessly find any applicable differences. Also, many kidney function biomarkers should be investigated precisely to diagnose and significant differences.

Authors' contribution

Hany A. Ibrahim, Salah M. Saleh, Hatem S. Mohammed, Mohamed Abdel-Bary and Abdelkader Ahmed Hashimand Ahmed F. Abdel-latif**,** all were responsible for study design and data gathering, data analysis. Mona M. Abdelmegidand Mohammed H. Hassan were responsible for laboratory workup and assessment and also shared in data and result analysis. All authors share in manuscript writing and approval of final version.

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