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RESEARCH ARTICLE
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Role of vitamin B3 in the prevention of acute kidney injury post-cardiac surgery through measurement of serum Cystatin C and Creatinine

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ABSTRACT

Background—Acute kidney injury is a risk factor for mortality in cardiac surgery patients. Nicotinamide adenine dinucleotide (NAD+) is a cofactor for numerous enzymes involved in cellular energy metabolism, and for adaptive responses of cells to bioenergetics and oxidative stress and is now a major player in aging and age-related diseases. Plasma cystatin C and creatinine have an important role in the early diagnosis of renal injury post-cardiac surgery.

Method: Using cohort - study design based on 90 subjects all patients subjected to open-heart surgery, were divided into two groups according to the dosing of niacin (vitamin B3) we measured serum cystatin C and creatinine basal level, one day before surgery, one day after surgery and after 7 days after surgery.

Results: Serum cystatin C level and creatinine significantly elevated ($p \leq 0.05$) in the second group (control group) (subjects who didn´t receive vitamin B3 supplement from baseline while those who receive vitamin B3 supplement show stable serum cystatin C and creatinine level.

Conclusion: vitamin B3 (niacin) has a beneficial role in renal protection after cardiac surgery.

Keywords: *vitamin, kidney, role, measurement.*

INTRODUCTION

Acute kidney injury (AKI) is one of the most frequent major complications of cardiac surgery, with increased risk of morbidity and mortality(1)(2)Cardiovascular death is 10–20 times more common in patients with renal impairment, and CVD is responsible for more than 40% of deaths of patients with end-stage renal disease (3)Even a slightly to severely reduced renal function increases the risk of CVD mortality and morbidity (4).

Injury of renal tubular epithelial cells is a universal feature of acute kidney injury, including the fact that the cause is unknown. Despite several clinical trials using a variety of treatments, finding a safe way to avoid acute kidney failure remains a challenge (5)

Niacin is known as vitamin B3, the third water-soluble vitamin being discovered, it plays a vital role in the overall development of the body, Niacin was first discovered by chemist Hugo Weidel in 1873 and extracted by Casimir Funk, but he thought it to be thiamine(6).

The nicotinamide coenzyme NAD+ is synthesized from four precursors that are provided in the diet: nicotinic acid, nicotinamide, nicotinamide riboside, and tryptophan.

NAD+ is synthesized from nicotinamide and nicotinamide riboside by two enzymatic reactions, while the pathway that produces NAD+ from nicotinic acid - known as the Preiss-Handler pathway — includes three steps. The kynurenine pathway is the longest NAD+ biosynthesis pathway: the catabolism of tryptophan through kynurenine produces quinolinic acid, which is converted to nicotinic acid mononucleotide, an intermediate in NAD+ metabolism. NAD+ is then synthesized from nicotinic acid mononucleotide by the Preiss-Handler pathway(figure 1) (7).

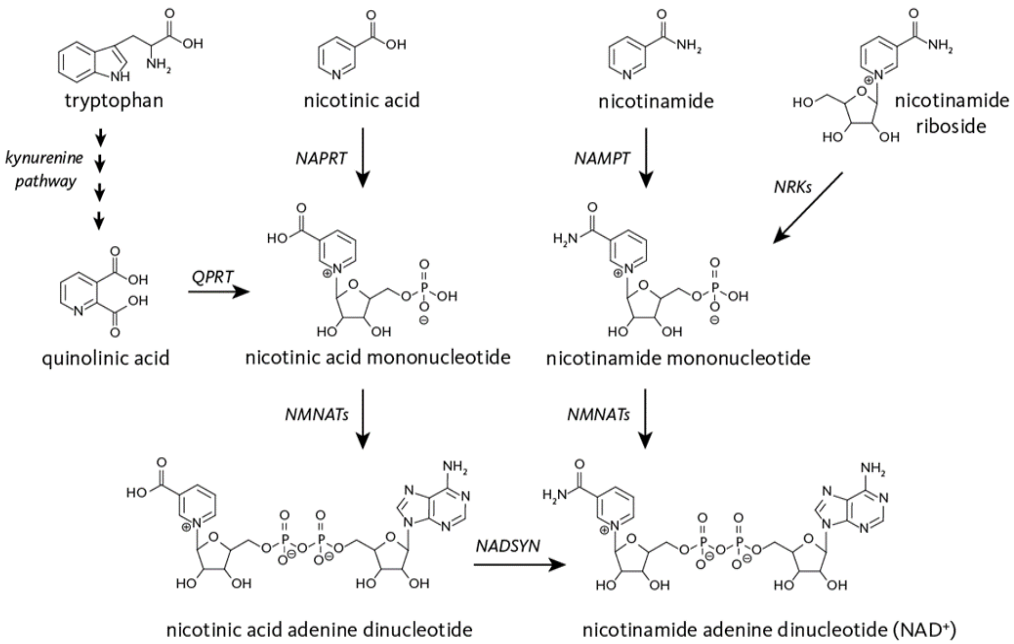

FIGURE 1: synthesis of Nicotinamide Adenine Dinucleotide (NAD+)

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Cystatin C is a protein that belongs to the cysteine protease inhibitors, cystatin family, that play an important role in the regulation of proteolytic damage to the cysteine proteases. Cystatin C is produced in the body at a constant rate in all nucleated cells. It is found in high concentrations in most body fluids, like in seminal fluid, cerebrospinal fluid (CSF), and synovial fluid (8).

Cystatin C is used as a marker of kidney functions for its relatively low molecular weight and easy detection to measure glomerular filtration rate (GFR) (9).

Cystatin C has a constant production rate, its concentration in serum is measured by (GFR) (10)(11). Since cystatin C is removed from the bloodstream by glomerular filtration, which is reduced in a state of decline in kidney functions that will lead to increased cystatin C concentration in serum(9). The benefit of cystatin C measurement is that its concentration is not changed by the presence of infections, liver diseases, or inflammatory diseases. The use of serum cystatin C as a marker of GFR is well documented, and some authors have suggested that it may be more accurate than serum creatinine for this purpose (12)(13).

Creatine is synthesized in the liver, kidneys, and pancreas, and is transported to its sites of usage, principally muscle and brain. About 1–2% of the total muscle creatine pool is converted daily to creatinine through the spontaneous, no enzymatic loss of water. Creatinine is an end-product of nitrogen metabolism, and as such undergoes no further metabolism, but is excreted in the urine by the kidney (20). Our study assesses if vitamin B3 has a role in the prevention and treatment of kidney injury after cardiac surgery.

SUBJECTS AND METHODS

Study design

This cohort-design study was conducted during the period from September 2019 to November 2020, the subjects were selected from Ibn Al-Bitar center for cardiac surgery in Baghdad –Iraq. The study is based on 90 subjects; 48 Male and 42 females; with age range (30-60 years) all subjects had cardiac problems and were subjected to open-heart surgery, they were divided into two groups according to the dosing of niacin (Vit B3).

The first group (45 subjects) receive vitamin B3 one week before the operation and one week after it, at a rate of one tablet (50 mg/day).

While the rest 45 patient considers as a control group (without any niacin dosage) the two groups matched in their age range and No of each sex (25,23 male & 20,22 female) in each group and that will be documented in the result.

Sample collection

Serum: vitamin B3, Cystatin C, and creatinine was measured for all subjects in basal level, one day before surgery, one day after surgery and after 7 days after surgery. (4 times of same measurements for all subjects, start dosing patients with vitamin B daily for 7 days before the date of the operation).

Blood samples were collected from all patients groups. The sample was drawn from the vein and stored by using a (5mL) disposable syringe.

The sample was divided into two parts both of them kept into dispensable tubes containing a gel which facilitate the separation processes of serum. The blood in the gel tube was allowed to clot at 37°C approximately at ten-fifteen min and then centrifuged at 4000 Xg for ten-fifteen min then the serum was divided into 2 parts and stored at (-20°C) until analysis (serum: vitamin B3, cystatin C, and creatinine).

Statistical analysis

Variables were expressed as mean ± SE, student's t-test was employed to compare the mean of normally distributed studied variables between two groups. The significant level which was dependent indifference and correlation is ≤0.05, more than it was considered as independent.

A receiver operating characteristic curve (ROC) curve is frequently used to show graphically the connection trades between clinical sensitivity and specificity for every possible cut-off for a test or a combination of tests (SPSS, version 26 was used).

RESULTS

The successful matching of groups in terms of matching their general status by mating (non-significant difference with p>0.05) subject´s age, sex, s.vitamin B3, s.Cystatin C and s.creatinine).

TABLE 1: Mean ± SE of age, Serum: Vitamin B3, Cystatin C, Creatinine of patients with a cardiac problem who were subjected to open cardiac surgery for both groups who were dosing (basal level) with vitamin B3 and not.

Parameter	Patient with cardiac problem subjected to open cardiac surgery will not be treated with Vit B3 No.45 Mean ± SE	Patient with cardiac problem subjected to open cardiac surgery will be treated with Vit B3 No.45 Mean ± SE	t.test Sig
Age (30-60) years	51.06 ± 1.64	52.82 ± 1.27	P > 0.05 N.S
Sex	1.45 ± 0.5	1.36 ± 0.49	P > 0.05 N.S
S.Vitmain B3 (ng/ml)	14.70 ± 1.34	16.26 ± 1.33	P > 0.05 N.S
S. Cystatin C (ng/ml)	34.850 ± 0.24	34.58 ± 0.23	P > 0.05 N.S
S. Creatinine (mg/dl)	0.80 ± 0.02	0.81 ± 0.02	P > 0.05 N.S

Start dosing patients with vitamin B3 (50 mg/day) for the first group for 7 days before the date of operation, and all parameters were followed for 7 days in the two groups and it was measurement a second time before the day of the operation.

A significant difference was found in the level of serum vitamin B3 which showed significant elevation in the group treated with vitamin B3, as was expected due to dosing.

TABLE 2: Mean ± SE of Serum: Vitamin B3, Cystatin C, Creatinine of patients with a cardiac problem whom subjected to open cardiac surgery for both groups whom dosing (1 day before operation) with vitamin B3 and not.

Parameter	Patients with cardiac problem whom will not be dosing with vitamin B3 after 7 days No.45 Mean ± SE	Patients with a cardiac problem who dosing with vitamin B3(50mg) after 7 days No.45 Mean ± SE	t.test Sig
S.Vitmain B3 (ng/ml)	14.70 ± 1.34	24.02 ± 1.06	P≤0.05 S
S. Cystatin C (ng/ml)	34.86 ± 0.24	34.6 ± 0.23	P > 0.05 N.S
S. Creatinine (mg/dl)	0.78 ± 0.02	0.81 ± 0.02	P > 0.05 N.S

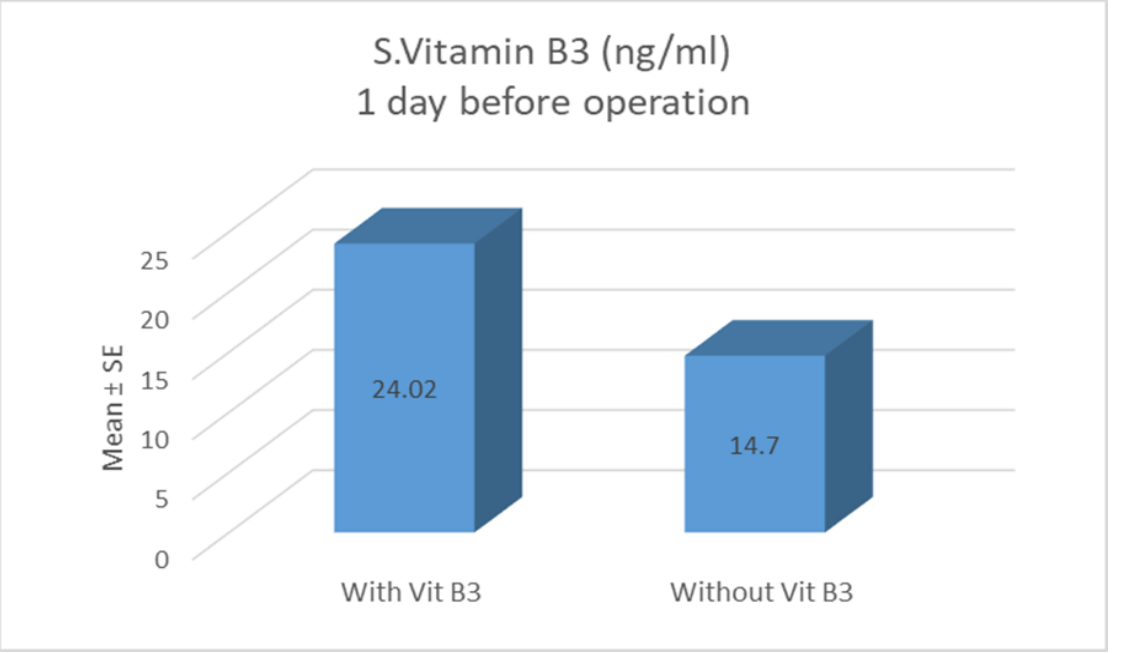

FIGURE 2: Mean difference between Patients with cardiac problem whom dosing with vitamin B3(50mg) after 7 days & Patients with cardiac problem whom was not dosing with vitamin B3 after 7 days according to vitamin B3($P \leq 0.05$).

TABLE 3: Mean ± SE of Serum: Vitamin B3, Cystatin C, Creatinine of patients with cardiac problem whom subjected to open cardiac surgery for both groups whom dosing (after 1 day of surgery) with vitamin B3 and not.

Parameter	The patient underwent open cardiac surgery whom dosing for 7 days with vitamin B3 after 1 day No.45 Mean ± SE	Patients underwent open cardiac surgery without any dosing of vitamin B3 after 1-day No.45 Mean ± SE	t.test Sig
S.VIT B3 (ng/ml)	20.26 ± 1.33	13.17 ± 0.85	p≤0.05 S
S. Cystatin C (ng/ml)	33.12 ± 0.22	34.64 ± 0.34	p≤0.05 S
S.Creatinine (mg/dl)	1.07± 0.05	1.15 ± 0.08	p>0.05 N.S

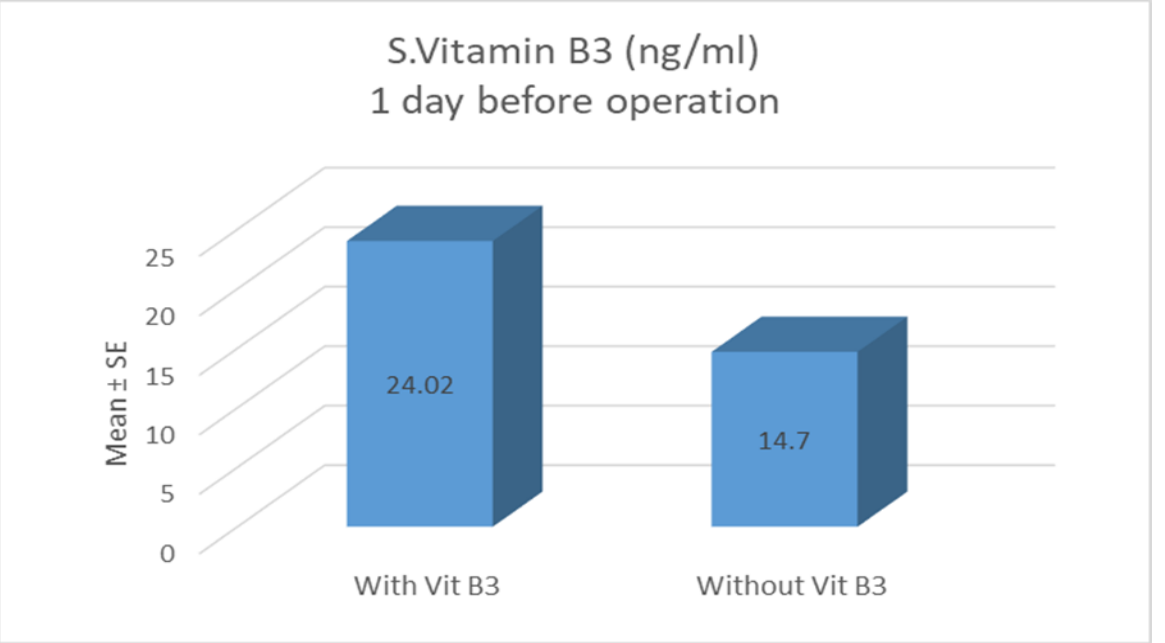

FIGURE 3: Mean difference between Patients with cardiac problem whom dosing with vitamin B3(50mg) after 7 days & Patients with cardiac problem whom will not be dosing with vitamin B3 after 7 days according to vitamin B3($P \leq 0.05$).

To follow up on the occurrence of acute kidney injury in those patients, and to shed light on the role of vitamin B3 dosing in the prevention of renal failure all measurements were repeated after 7 days while continuing to give the same dose of vitamin B3 (50 mg/day) for 7 days. It was found that Table (3)

TABLE 4: Mean ±SE of Serum: Vitamin B3, Cystatin C, Creatinine of patients with cardiac problem whom subjected to open cardiac surgery for both groups whom will dosing (after 7 days of surgery) with vitB3 and not.

Parameter	The patient underwent open cardiac surgery whom dosing for 7 days with vitamin B3 of after 7 days No.45 Mean ± SE	Patients with open cardiac surgery without any dosing of vitamin B3 after 7 days No.45 Mean ± SE	t.test Sig
S.Vitmain B3 (ng/ml)	27.47 ± 0.8	13.23 ± 1.02	p≤0.05 S
S. Cystatin C (ng/ml)	35.52 ± 0.34	36.74 ± 0.24	p≤0.05 S
S.Creatinine (mg/dl)	0.84 ± 0.03	0.99 ± 0.06	p≤0.05 S

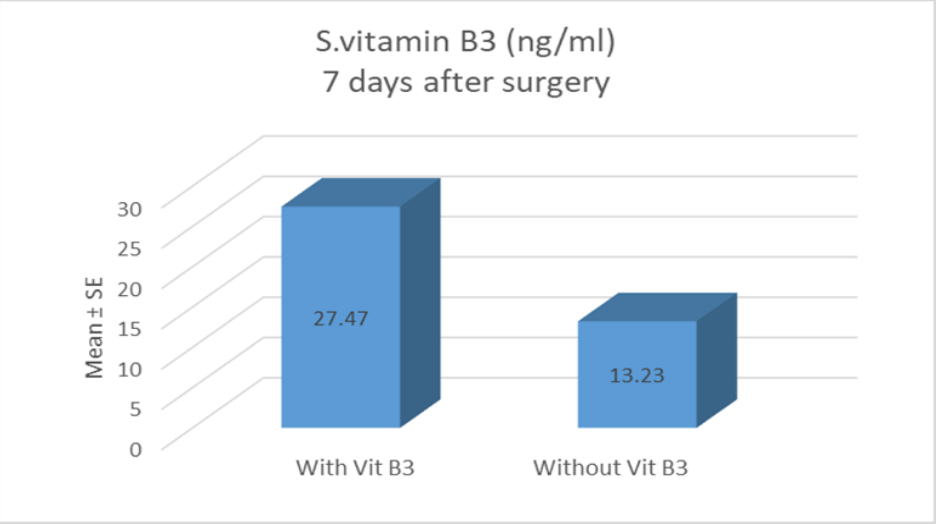

FIGURE 4: Mean difference between Patient who underwent open cardiac surgery who dosing for 7 days with vitamin B3 after 7 days & Patients with open cardiac surgery without any dosing of vitamin B3 of after 7 according to vitamin B3 (P≤0.05).

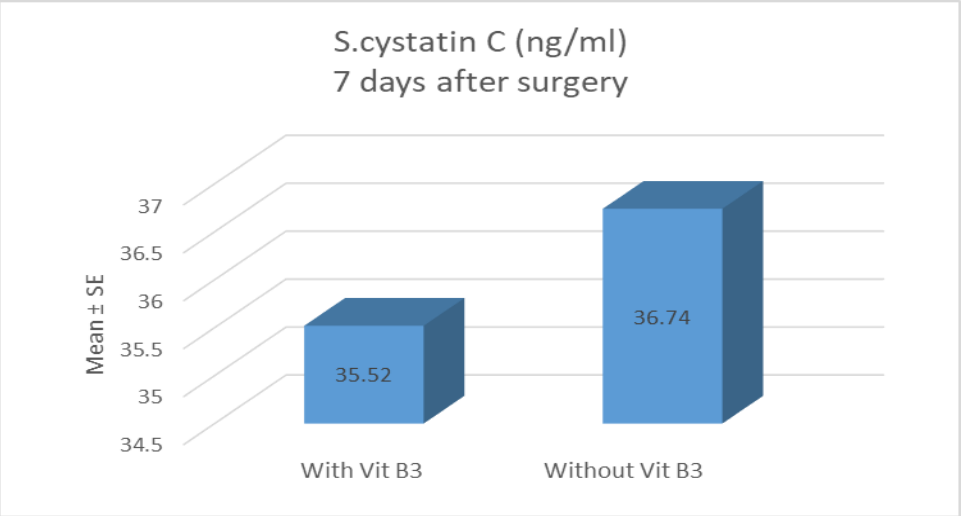

FIGURE 5: Mean difference between Patient who underwent open cardiac surgery who dosing for 7 days with vitamin B3 after 7 days & Patients with open cardiac surgery without any dosing of vitamin B3 of after 7 according to Cystatin C (P≤0.05).

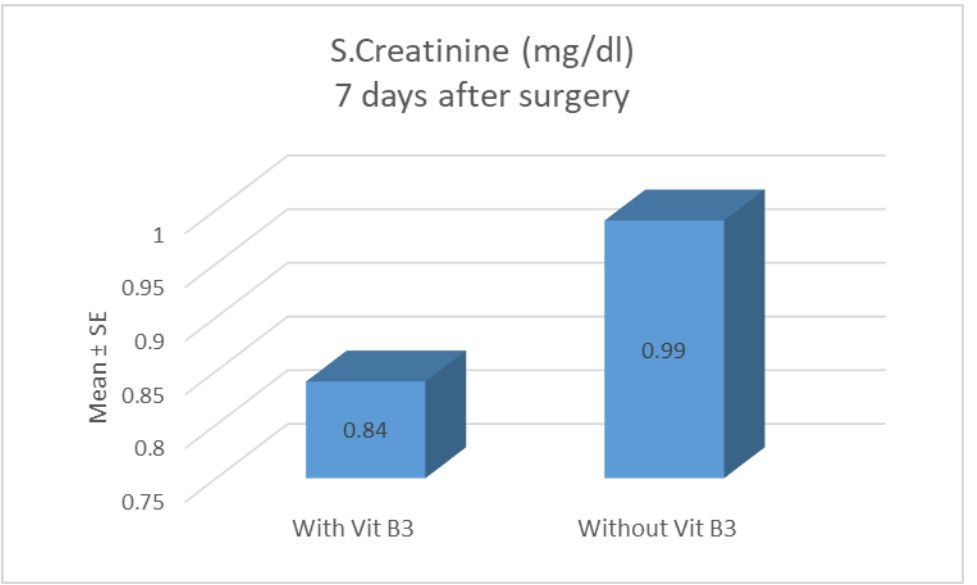

FIGURE 6: Mean difference between Patient who underwent open cardiac surgery who dosing for 7 days with vitamin B3 after 7 days & Patients with open cardiac surgery without any dosing of vitamin B3 of after 7 according to s.creatinine (P≤0.05).

TABLE 5: Sensitivity and specificity, the area under and cut-off point of studied kidney marker S. Cystatin C

Parameter	Sensitivity	Specificity	AUC	Cut-off
S.Cystatin C	84.85	69.70	75	>35.564

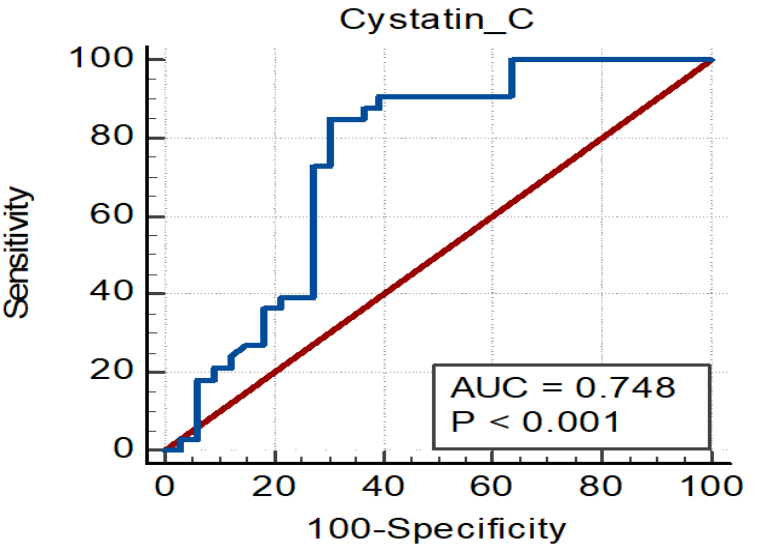

FIGURE 7: ROC curve of sensitivity and specificity, the area under and cut-off point of CystatinC.

DISCUSSION

In the table (1), subjects age and sex-matched that, Acute kidney injury seems to be not significantly different in our study age groups (30-60) because elderly (>65) subject is at higher risk of developing AKI and have the worse outcome (19).

No significant sex difference in the susceptibility of acute kidney injury after cardiac surgery in our study, so "sex" is not associated with contrast-induced nephropathy (CIN) (14).

All subjects had normal basal vitamin B3 level (> 16) determined by ROC and the absence of AKI has been confirmed in all subjects by measuring the level of (serum Creatinine and Cystatin C) and results matched in both groups.

In table (2) serum vitamin B3 level showed to be significantly increased ($p \leq 0.05$) (24.02±1.06) in subjects who received vitamin B3 supplements for one week before cardiac surgery and this result is considered to be normally occurring after dosing.

Vitamin B3 (niacin) has an important role in maintaining normal renal function through a different mechanism including energy production by mitochondria which present in the heart and kidneys in the highest numbers and they are among the greatest oxygen consumers of all organs in the body(15).

Energy production is maintained in these organs through the oxidative metabolism of a range of fuels, substrate metabolism is strongly tied to the pyridine dinucleotide, nicotinamide adenine dinucleotide (NAD+), this essential metabolite serves as a key cofactor in mitochondrial metabolic processes that facilitate energy production(16) and also has several other important cellular functions(17).NAD+ is a hydride acceptor that forms the reduced dinucleotide NADH. The NAD+/NADH nucleotide pair is vital for driving reduction-oxidation (redox) reactions in energy production. Furthermore, NAD+ is a precursor for the phosphorylated dinucleotide pair NADP+/NADPH, which is required for several cellular biosynthetic pathways and to protect cells from reactive oxygen species (ROS), also NAD+ acts as an enzyme-substrate for several non-redox reactions, such as those that occur in signaling pathways(18)

It was noticed that after a day of the open cardiac surgery, the patients who were not dosed with vitamin B3 (table 3) showed an increase in the level of serum cystatin C which indicate a defect in the function of the kidneys, despite the serum level of creatinine remain with a normal level and table (4) serum cystatin C, creatinine, significantly increased ($p \leq 0.05$) (36.74 ± 0.24) (40.45 ± 2.7)

respectively one week after surgery which increases the risk of AKI in those who didn´t receive vitamin B3 supplement, while those who received vitamin B3 supplements show a significant increase ($p \leq 0.05$) (27.47±0.8) in serum niacin level with stable serum cystatin C and creatinine.

When it comes to detecting acute kidney damage, serum Cystatin C (CyC) is more sensitive than creatinine. The CyC rise hits maximum levels in 24 hours following exposure to contrast. Also released in circulation with a half-life of about 2 h, CyC, which is made by all nuclear cells and filtered and catabolized freely into proximal tubules without being secreted. In other words, the serum concentration is measured by the glomerular filtration process and is thus accepted as a GFR (19)

In critically ill patients, serum cystatin C level was also shown to diagnose AKI 1-2 days before creatinine level, and postoperative cystatin C level was more successful at detecting AKI in cardiac surgery patients (20)

Kidner injury after cardiac surgery (increase serum Cystatin C and creatinine) has different mechanisms including mechanical trauma caused by blood pumping (centrifugal pumps, which are now almost exclusively used as the primary pump during cardiopulmonary bypass, have been shown to improve some markers of renal function compared with roller pumps) (21), oxygenator turbulence, cardiotomy suction, and cell saver use, cardiopulmonary bypass is associated with hemolysis and the generation of free hemoglobin and iron (22), all of which contribute to the production of oxidative stress and renal injury(23). Specifically, hemoglobin subjected to hydrogen peroxide or superoxide may release free iron into the circulation, which then participates in biochemical reactions, resulting in hydroxyl formation and tissue damage(24).

In table (5) Through the ROC analysis, the ability of serum cystatin C as a test to correctly identify patients with a disease was determined bud the results showed that the test had moderate sensitivity for the diagnosis of an early kidney failure, while the ability of the test to correctly identify people without the disease (specificity) also showed that the test had moderate specificity for the diagnosis of AKI. This can also give another explanation for the lack of relationships with the state of kidney failure or its clarity during this period.

Strengths and limitations

Our study is notable for its prospective and detailed assessment of a carefully selected cohort of subjects with normal preoperative renal function, and with no AKI, any subject with a risk factor for renal impairment was excluded. Our study has limitations that need to be considered when interpreting the results that our study was interrupted by the pandemic of COVID-19 so elective surgeries were postponed and difficulty in movement during the lockdown, and the consequence of the delay in obtaining the Kits and chemicals needed.

On the other hand side effect of niacin such as redness and itching obligate us to minimize the dose to 50 mg/day.

CONCLUSION

vitamin B3 (niacin) show a significantly beneficial role in renal protection after cardiac surgery by assessing S.Cystatin C and S.Creatinine level post cardiac surgery.

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