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Role of Vitamins and Trace Elements on Renal Function of Septic Pediatrics on a Nephrotoxic Drug

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Abstract: Septic acute kidney injury (AKI) makes up roughly half of all such AKI. Serum creatinine (Sr.cr) and urine output (U.O.P) with clinical evaluation serve as the basis for the diagnosis. Vitamin and trace elements may be beneficial for AKI, So, we assessed their impact on the kidney functions of septic pediatrics utilizing nephrotoxic antibiotics in their treatment regimen by assessing Sr.cr, Cr.cl, U.O.P, and Serum Cystatin C (SCysC) as kidney biomarker. 43 pediatrics were randomized into two groups, a control group and an interventional group (supplemented with vitamin and trace elements). Each group was assessed at a baseline, 24 and 72 hrs. from the start of their treatment. Result: We compared the results at a baseline and after 72 hrs., in the interventional group: Cr.cl was significantly increased by 1.25 folds from the baseline (P=0.007) while the fold increase was 1.1 only in the control group (P=0.055). Also, Sr.cr showed a statistically significant decrease by 1.6 folds in the interventional group (P= 0.001) while in the control group was (P= 0.038). Also, blood urea nitrogen (BUN) decreased by 1.3 and 1.6 folds in interventional & control groups respectively. The same significant changes were seen in U.O.P in both groups. SCysC was no statistically significant change in the control and interventional group (P=0.268), (P=0.277) respectively. In conclusion, Vitamin and trace elements show promising roles in improving Cr.cl (not Sr.cr, U.O.P, nor SCysC), So, they may reduce the risk of AKI in septic pediatrics treated with nephrotoxic antibiotics.

Keywords: AKI, Vitamins, Trace elements, Creatinine clearance, Serum Cystatin C, Nephrotoxic drug.

1. INTRODUCTION

There are consensus definitions of acute kidney damage (AKI) and sepsis. Septic AKI is identified by the simultaneous occurrence of both. Septic AKI syndrome predominates and causes around half of wholly such AKI that happen in the unit of intensive care. Although the pathophysiology of septic AKI is still poorly known, the deficiency of histopathological differences suggests that Septic AKI may, at least initially, be a functional occurrence that is accompanied by tubular cell damage and microvascular shifting. Its identification is still established on the patient clinical valuation, the amount of urine produced, and serum creatinine.[1] AKI early recognition in severe sepsis is essential to provide the best treatment for the avoidance of more kidney injury especially during using a nephrotoxic antibiotic. AKI diagnosis criteria have undergone three restructures to more accurately and earlier identify the severe condition: the standards of RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease) were initially established in 2004, followed by the standards of AKIN (Acute Kidney Injury Network) in 2007, and most recently KDIGO (Kidney Disease Improving Global Outcomes) standards in 2012.[2-4] Serum creatinine (Sr.cr) and urinary output are utilized as the three benchmarks for evaluating kidney function.[5] Nevertheless, when utilized to diagnose AKI, serum creatinine, and urine output have several limitations.

Severe sepsis diminishes muscle perfusion, which results in decreased creatine synthesis. This

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prevents AKI from being quickly identified and dulls the increase in serum creatinine level, Therefore, due to decreased creatinine production and the dilutional effects of intensive fluid resuscitation in cases of septic shock, AKI may be misdiagnosed as a kidney injury in sepsis.[6] Because urine output and Sr.cr are famed for being non-specific and insensitive indicators of renal function, it has been suggested that serum cystatin c is a more accurate indicator of glomerular filtration rate than serum creatinine.[5] Serum Cystatin C varies before Sr.cr once renal function starts to change[7-8] and it is still the best indicator of renal function in CKD patients.[9-10] There is still controversy over whether it is a reliable indicator of AKI. But there a meta-analysis revealed that Serum Cystatin C displays a respectable diagnostic routine for expecting all-cause AKI.[11] Avoidance of septic acute kidney injury is still established through early resuscitation (usage of vasoactive medications along with fluids) and the treatment of sepsis. Particularly, there is great proof that fluids with starch are toxic to the kidney and impair its function, and fluids with chloride can do so.[1] Also postponed antibiotics administration in septic shock was linked with quick AKI development.[12] Antioxidants, both exogenous and endogenous, avoid oxidation, inflammation, and kidney damage in AKI. For instance, nephrotoxicity is reduced by selenium, which can boost the activity of antioxidant enzymes that depend on GSH.[13] Acute kidney injury (AKI) treatment options include antioxidants (vitamins and trace elements) that lower ROS or increase the body's antioxidant supply.[14]

2. METHODS

A parallel, open-labeled, randomized, prospective, controlled trial was conducted in this instance. Enrolled study subjects: Forty-three pediatric patients from Cairo University's Children's Hospital's (Abu-Elrish Hospital) intensive care units, participated in this study, between (March) 2020 (and June) 2021 after authorization from the medical ethical committee of Cairo University, Cairo, Egypt, code: S-24-2019 on 12 February 2020.

2.1. Randomization, masking, and drug administration:

The randomization method used in our study was a simple randomization method through making blinded papers hold the symbol I (Interventional group) or C (Control group) and choosing one paper randomly for every participant in the study a person from outside the study. Twenty pediatric patients made up the control group, who did not get vitamins or trace elements, whereas 23 pediatric patients made up the interventional group received vitamins and trace elements. Vitamins and trace elements were intravenously administered in glucose 5% solution over 6-8 hours every day for 3 days from the start of the study. According to what has been described in the literature, the vitamin and trace element doses were chosen (pamphlet of the manufacturer Fresenius Kabi Company) and it was given according to the weight of each pediatric patient; Soluvit N (IV Water-soluble vitamins) was given by calculation the dose. Patients weighing ≥10 Kg were administered one vial while patients weighing <10 Kg take 1/10 of the content of one vial/kg/day on glucose 5% solution over 6-8 hours covered from the light while Addamel N (IV Trace elements) dose given according to the weight of each pediatric patient, 0.1 ml addamel N/kg/day on glucose 5% solution over 6-8 hours.

2.2. Sampling for nephrotoxic antibiotic leveling (Vancomycin):

Vancomycin trough levels for each patient were measured to make sure they were within the therapeutic range for the intended effect and to avoid subtherapeutic and toxic levels that could have an impact on the therapeutic outcomes and perhaps cause nephrotoxicity. Timing of initial vancomycin trough levels was done just before 30 minutes of the 4th dose of vancomycin if it was given every 8 hours or just before 30 minutes of the 5th dose of vancomycin if it was given every 6 hours).

2.3. Materials:

- Soluvite N (IV Water-soluble vitamins) produced by the Fresenius Kabi Company, Lot no: 10qi1176.
- Addamel N (IV Trace elements) produced by the Fresenius Kabi Company. Lot no: 63323-143.
- Cystatin C: Kit Cobas (Tina-quant Cystatin C Gen.2), Lot No: k080811, Product Code: 510(k).
-Vancomycin kit: SEIMENS Emit®2000 vancomycin assay, BATCH/LOT (10) P4, VIVA pro E instrument of SEIMENS for vancomycin leveling.

2.4. Methods:

Three milliliters of blood were drawn from each patient, (at baseline time, after 24 hours, and after 72 hours) from the start of the treatment. At 936 g and 4 °C, the blood samples were centrifuged for 20 min. The serum was divided into two or three aliquots and kept at 80 °C until it was time for analysis. The kit's instructions state that, serum Cystatin C was quantified and measured. Vancomycin trough level was determined by quantitative analysis following the kit method utilizing SEIMENS' VIVA pro-E instrument.

2.5. Statistical analysis:

The Statistical Package of Social Science Software Program, version 25 (IBM SPSS Statistics

for Windows, Version 25.0, Armonk, NY: IBM Corp.), was used to enter the data and perform the statistical analysis. For quantitative data, the mean, standard deviation, median and interquartile range were used; for qualitative variables, frequency and percentage were used.

When comparing groups based on qualitative variables, Chi-square or Fisher's exact tests were used; when comparing groups based on quantitative data, the Mann-Whitney test was used. The Wilcoxon test was used to see how different parameters changed over time. Statistical significance was defined as P values of 0.05 or less.

3. RESULTS

In this clinical trial, forty-three pediatric patients were enrolled, 20 of whom were in the control group (had no supplements), and 23 pediatric patients in the interventional group (had vitamins and trace elements supplements) both groups were matched at a baseline where statistically, the two groups were not significantly different from one another regarding their demographic data, source of infection, antibiotics used, kidney functions, and antibiotic trough level where all P values were more than 0.05 as illustrated in the **table (1) & (2).**

When comparing the laboratory parameters within each group at a baseline and after 72 hrs., our results showed that: U.O.P increased significantly within both groups (P value= 0.003, 0.000) in the interventional and control group respectively. The decrease in Sr.cr within the interventional group (1.6 fold) was more statistically significant than the control group (P value= 0.001*, 0.038*) in the interventional and control group respectively. The same improvement was noticed in BUN which was more statistically significant in the interventional group than the control group (P value= 0.002*, 0.046*) in the interventional and control group respectively. The results of the creatinine clearance were surprising, where it was highly significantly increased by 1.25 folds from the baseline results while the fold increase was 1.1 only in the control group, as illustrated in **Figure (1).** As regards serum Cystatin C: statistically from a baseline to after 72 hrs., both groups were not significantly significantt, the interventional group (P=0.277) and the control group (P=0.268), as illustrated in **Table (3).**

The results demonstrate a comparison between the two groups' results after 24 and 72 hours regarding kidney functions: In interventional group had an approaching statistically significant increase in Cr.cl after 72hrs. (P-value=0.054) comparable with the control group, the urine output (P-value=0.618), and the serum Cystatin C (P-value=0.685) i.e. statistically, the two groups were not significantly different as illustrated in **Table (4)** and **Figures (2-6).**

Table 1. Comparison between the study groups according to the demographic data at baseline.

Demographic data	Interventional group (n=23)	Control group (n=20)	P value
Sex			
Male No (%)	12 (52%)	12 (60%)	**0.606**
Female No (%)	11 (48%)	8 (40%)	
Age (y) Mean ± SD	8.7 ± 3.4	7.3 ± 3.3	**0.225**
Weight (Kg) Mean ± SD	30.7 ± 17.6	20.9 ± 8	**0.083**
Height (cm) Mean ± SD	125.7 ± 25.2	114.6± 17.5	**0.095**

SD: standard deviation, **n**: number of patients. **P-value** > 0.05: non-significant. All data were represented as mean ± SD, **Interventional group**: patients who were supplemented with vitamins and trace elements with their antibiotics regimen (empirically or culture based).**Control group**: patients who were received their antibiotics regimen (empirically or culture based) only.

4. DISCUSSION

The study's objective was to assess how vitamins and trace elements affected septic pediatric patients using nephrotoxic antibiotics by kidney function monitoring as serum creatinine, creatinine clearance, and serum Cystatin C as renal biomarkers where the nephrotoxic antibiotic (vancomycin) was used as a part of treatment regimen in two groups. Early resuscitation (prudent use of both fluids and vasoactive medications) and treatment of sepsis are still the mainstays in avoiding the development of septic AKI).[1] In our study empirical antibiotics (including vancomycin) were early administered with another empirical antibiotic plus lactated ringer

and norepinephrine (NE) were used in the resuscitation of the cases in the two groups to decrease the incidence of AKI. Numerous studies have shown that monitoring the vancomycin trough level in children with Gram-positive septic shock can increase clinical efficacy and decrease nephrotoxicity, much like it does in adults.[15-17]

Table 2. Comparison between the study groups according to the source of infection, antibiotics used at baseline, kidney functions, and antibiotic trough level at baseline.

At baseline Data	Interventional group (n=23)	Control group (n=20)	P value
Source of infection			
Blood N (%)	16 (70%)	8 (40%)	**0.155**
Chest N (%)	5 (21%)	6 (30%)	
Wound N (%)	2 (8%)	4 (20%)	
CNS N (%)	0 (0%)	2 (10%)	
Antibiotics used at baseline			
Vancomycin + Meropenem n(%)	21 (91.3%)	18 (90%)	**0.566**
Vancomycin + imipenem/cilastatin n(%)	1 (4.3%)	0 (0%)	
Vancomycin + Meropenem n(%)			
Vancomycin + cefepime hydrochloriden (%)	1 (4.3%)	1 (5%)	
Vancomycin + ceftriaxone sodium n (%)	0 (0%)	1 (5%)	
Kidney functions			
U.O.P (mL/kg/hour) Mean ± SD	1.9 ± 1	1.9 ± 0.7	0.705
Scr (mg/dL) Mean ± SD	0.8 ± 1	0.6 ± 0.3	0.364
BUN (mg/dL) Mean ± SD	25.3 ± 22.3	26 ± 22	0.635
Cr.cl (mL/min) Mean ± SD	90.6 ± 57	73.8 ± 31.7	0.443
Serum Cyctatin C (mg/L) Mean ± SD	0.9 ± 0.5	0.8 ± 0.4	0.480
Antibiotic trough level			
Vancomycin trough level (mcg/mL) Mean ± SD	6.8 ± 1.3	7 ± 1.1	0.715

CNS: central nervous system, **U.O.P**: Urine Out Put, **Sr.cr**: Serum creatinine, **BUN**: Blood Urea Nitrogen, **Cr.cl**: Creatinine clearance, **SD**: standard deviation. All data were represented as mean ± SD. **P-value** > 0.05: non-significant. **Interventional group**: patients who were supplemented with vitamins and trace elements with their antibiotics regimen (empirically or culture based). **Control group**: patients who were received their antibiotics regimen (empirically or culture based) only.

The serum trough level of vancomycin should be controlled, according to clinical treatment guidelines, To achieve the goal AUC24/MIC 400, IDSA guidelines 2009 advise aiming for trough levels of vancomycin 15-20 mg/L in both pediatric and adults as well,[18] but further study found that, In critically ill children vancomycin trough concentration associated with the AUC24 of 400 was much lower than that in adults.[19] Vancomycin has a variety of potential goals depending on the population under consideration; nevertheless, troughs of 6–10 mg/L are probably adequate to achieve an AUC/MIC of 400 for pediatric patients.[20] The therapeutic trough concentration for neonates or pediatric patients is therefore 5–15 mg/L according to China's pharmacological association 2020 guideline.[21] And this range resembles that observed in our patients.

Nephrotoxicity and ototoxicity rates peaked at vancomycin trough concentrations >15 g/mL, were then followed by concentrations between 10 and 15 g/mL, and the lowest incidence was seen at concentrations below 10 g/mL.[22]

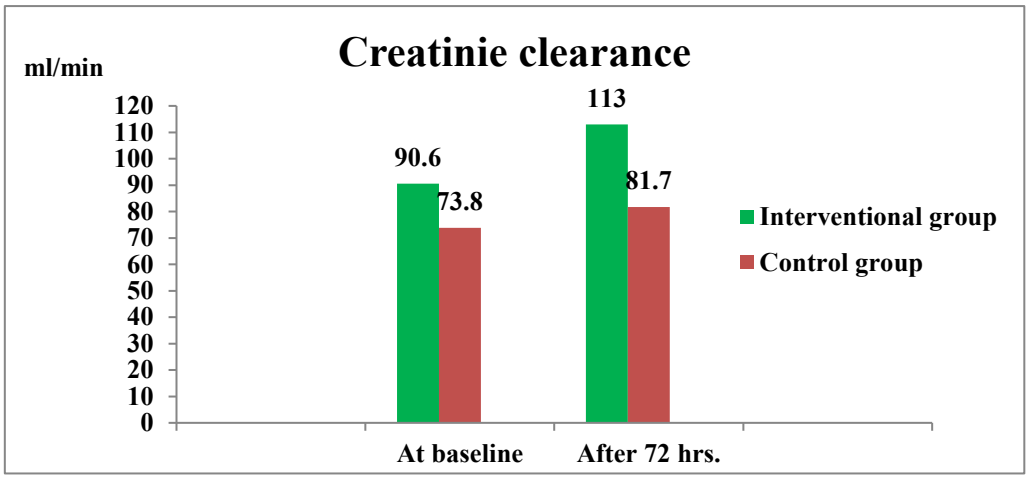

Figure 1. Creatinine clearance among interventional group and control group at baseline and 72 hrs. from starting standard antibiotic regimen.

Table 3. Change of kidney functions at a baseline and after 72 hours within each group separately:

Kidney functions	Interventional group (n=23)		P value	Control group (n=20)		P value
	At baseline	After 72 hrs.		At baseline	After 72 hrs.	
U.O.P (Mean ± SD)	1.9 ± 1	2.7 ± 1	**0.003***	1.9± 0.7	2.8 ± 0.8	**0.000***
Sr.cr (Mean ± SD)	0.8 ± 1	0.5 ± 0.3	**0.001***	0.6± 0.3	0.6 ± 0.7	**0.038***
BUN (Mean ± SD)	25.3± 22.3	19 ± 14.8	**0.002***	26 ± 22	16.6± 11.6	**0.046***
Cr.cl (Mean ± SD)	90.6 ± 57	113± 57.6	**0.007***	73.8±31.7	81.7± 30	**0.055**
Serum Cyctatin C (Mean ± SD)	0.9 ± 0.5	0.8 ± 0.3	**0.277**	0.8± 0.4	0.8 ± 0.4	**0.268**

U.O.P: Urine Out Put, **Sr.cr**: Serum creatinine, **BUN**: Blood Urea Nitrogen, **Cr.cl**: Creatinine clearance, **SD**: standard deviation, *: statistical significant, **p-value** < 0.05, **P-value** > 0.05: non-significant. All data were represented as mean ± SD. **Interventional group**: patients who were supplemented with vitamins and trace elements with their antibiotics regimen (empirically or culture based). **Control group**: patients who were received their antibiotics regimen (empirically or culture based) only.

Also, trough levels of vancomycin >15 mg/ml also seem to be linked to a three times higher risk of nephrotoxicity in a prospective multicenter trial. Thirteen patients (8.9%) with trough levels of 15 mg/ml and forty-two patients (29.6%) with concentrations >15 mg/ml had nephrotoxicity.[17] In our study, the baseline trough level of vancomycin in the two groups was <10mg/ml. In the interventional group, it was 6.8 ± 1.3 although, it was 7 ± 1.1 in the control group and these levels represent the lowest incidence of nephrotoxicity and ototoxicity. Several studies clear the effect of vitamins and trace elements on kidney functions. In a study by Moskowitz A, et al., it was discovered that compared to placebo patients, septic shock patients receiving thiamine had lesser creatinine levels in their serum and less chance of development to kidney replacement therapy. This randomization trial reveals that the greater incidence of renal damage in the placebo group may be caused by mechanisms besides decreased blood flow to the kidney. Thiamine deficiency has been associated with an increase in apoptosis in cardiac myocytes, vascular endothelium, retinal pericytes, and neurons. According to Moskowitz A. et al., thiamine administration may have prevented renal tubular cells from dying due to apoptosis.[23] Vitamin C does seem to alleviate kidney damage and vascular damage in sepsis, and it displays hopeful reno-protection in AKI.[24-25]

Table 4. Comparison between both groups after 24 and 72 hour regarding kidney functions.

	Interventional group (vitamin and trace elements group) (n=23)	**Control group (No supplement group) (n=20)**	**P value**
U.O.P (mL/kg/hour)			
After 24 hrs Mean ± SD	1.9 ± 1	1.9 ± 0.7	**0.609**
After 72 hrs Mean ± SD	2.7 ± 1	2.8 ± 0.8	**0.480**
Sr.cr (mg/dL)			
After 24 hr Mean ± SD	0.8 ± 1	0.6 ± 0.3	**0.394**
After 72 hrs Mean ± SD)	0.5 ± 0.3	0.6 ± 0.7	**0.842**
BUN (mg/dL)			
After 24 hrs Mean ± SD	25.3 ± 22.3	26 ± 22	**0.679**
After 72 hr Mean ± SD	19 ± 14.8	16.6 ± 11.6	**0.618**
Cr.cl (mL/min)			
After 24 hr Mean ± SD	90.6 ± 57	73.8 ± 31.7	**0.450**
After 72 hr Mean ± SD	113 ± 57.6	81.7 ± 30	**0.054****
Sr. Cyctatin C (mg/L)			
After 24 hrs Mean ± SD	0.9 ± 0.5	0.8 ± 0.4	**0.436**
After 72 hrs Mean ± SD	0.8 ± 0.3	0.8 ± 0.4	**0.685**

U.O.P: Urine Out Put, **Sr.cr**: Serum creatinine, **BUN**: Blood Urea Nitrogen, **Cr.cl**: Creatinine clearance, **SD**: standard deviation, **: approaching statistical significant, p-value near 0.05 All data were represented as mean ± SD. **Interventional group**: patients who were supplemented with vitamins and trace elements with their antibiotics regimen (empirically or culture based). **Control group**: patients who were received their antibiotics regimen (empirically or culture based) only. **P-value** > 0.05: non-significant.

Immediate intravenous injection of thiamine, hydrocortisone, and vitamin C has been shown in an observational study of sepsis to help in avoiding continuous organ damage, particularly acute damage to the kidneys, and in reducing patients' mortality from fatal sepsis and also septic shock.[26]

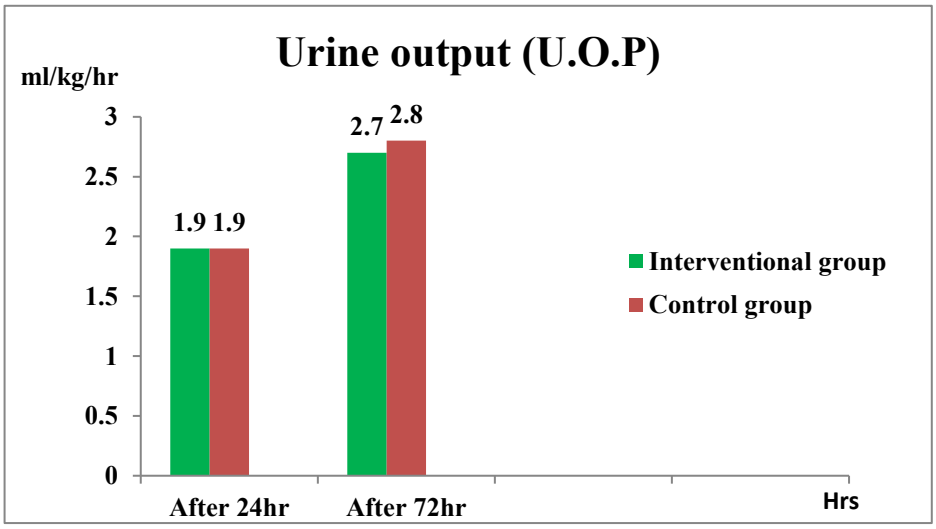

Figure 2. Urine output among interventional group and control group after 24hr and 72 hrs. from starting standard antibiotic regimen.

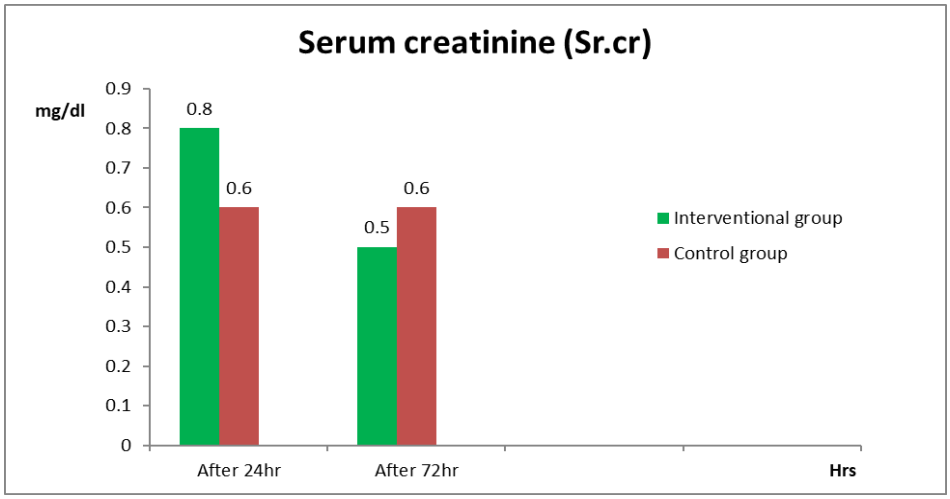

Figure 3. Serum creatinine among interventional group and control group after 24hr and 72 hrs. from starting standard antibiotic regimen.

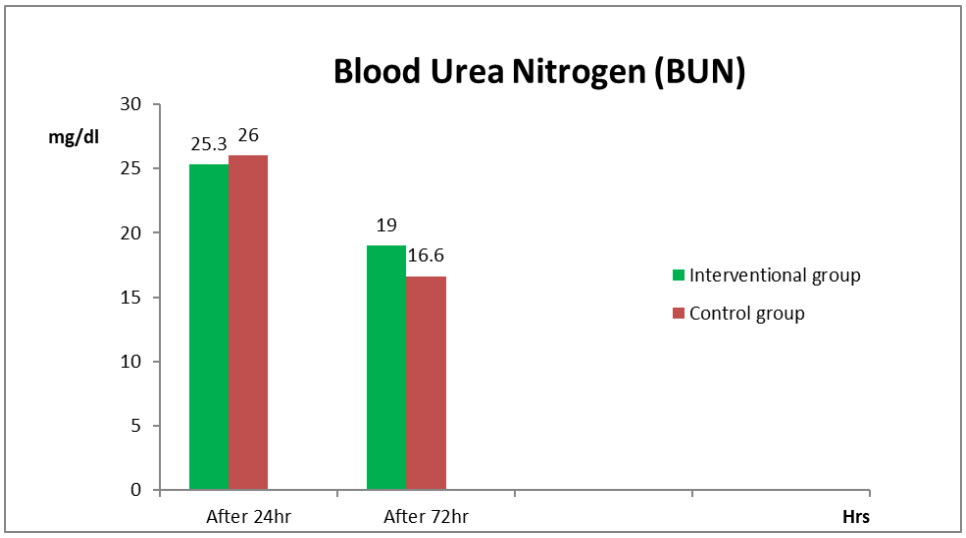

Figure 4. Blood urea nitrogen among interventional group and control group after 24hr and 72 hrs. from starting standard antibiotic regimen.

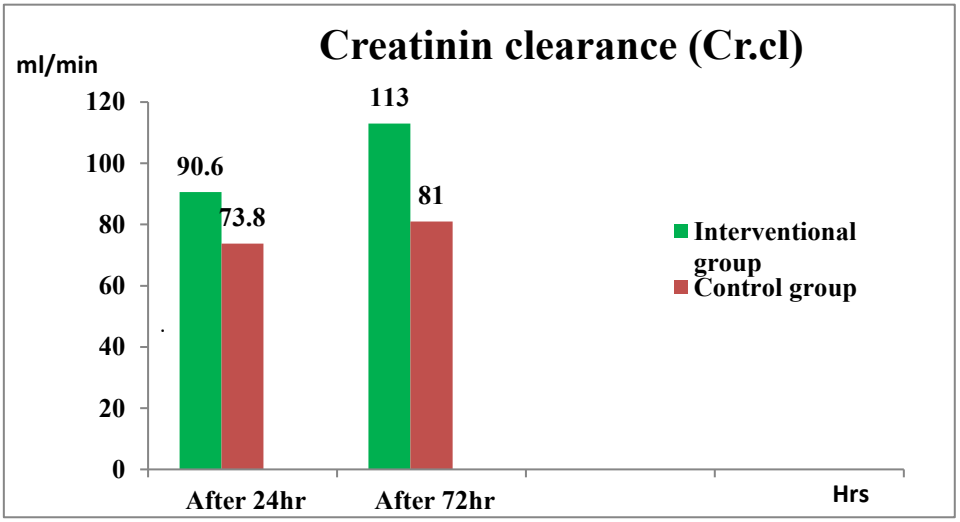

Figure 5. Creatinine clearance among interventional group and control group after 24hr and 72 hrs. from starting standard antibiotic regimen.

Another study indicates that the overall population's kidney health may be defended by iron because mitochondrial proteins contain cofactor

iron/sulfur complexes, increased cellular iron accessibility may be necessary.[27] However, if it builds up above what is normal for cells, superoxide produced by the respiratory chain in the mitochondria may cause the flow of toxic free iron from ferrous/sulfur complexes, this is another reason for reactive oxygen species.[28] A meta-analysis on renal function revealed that measuring blood cystatin c at baseline, after 12 hours, after 24 hours, and after 48 hours results in exhibits a reasonable diagnostic performance for anticipating all-cause AKI. Foremost, the best time to draw a blood sample appears to be 24 hours after the first sign of acute kidney injury, having 0.82 sensitivity and 0.83 specificity.[11]

Moreover, when serum Cystatin C in blood was compared to diagnosing AKI in a different meta-analysis, it was discovered that Serum Cystatin C proved to be a superior biomarker for AKI prediction, early serum Cystatin C remains of diagnostic utility is obtained throughout twenty-four hours of damage to the kidneys or admission to ICU.[29] Also in our study cystatin c was measured at baseline, after 24hr and after 72hr from intensive care unit admission, the patients were at low risk to develop AKI, and serum cystatin c (SCysC) in the treated showed no statistically significant difference between baseline and after 72 hrs. (P=0.277) also in control group SCysC showed no statistically significant difference (P=0.268) and that may be due to the vancomycin trough level in both group was in a low normal range.

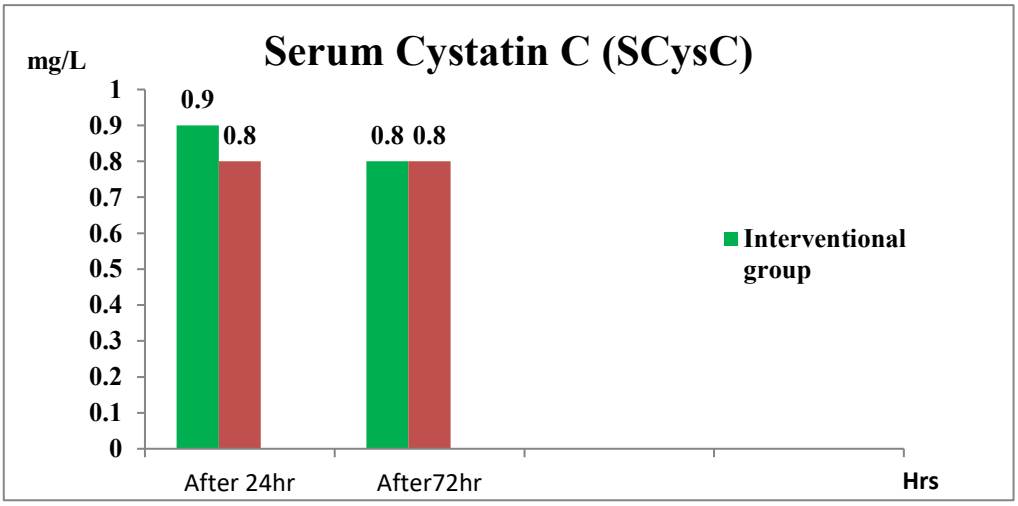

Figure 6. Serum Cystatin C among interventional group and control group after 24hrs. and 72 hrs. from starting standard antibiotic regimen.

Serum Cystatin C levels after 72 hours did not statistically differ between the two groups when we compared them in our study (P=0.685), which mean no effect of vitamin and trace elements on the SCysC as kidney function biomarker and that may be due to measuring Cystatin C after short-term duration usage of vitamins (72hr), In contrast, what happened in a randomized controlled trial, when patients with microalbuminuria received vitamin B complex supplements for 12 weeks saw an improvement in renal function (Cystatin C) and a significant drop in homocysteine levels compared to baseline levels (p 0.001), baseline Cystatin C was negatively linked with vitamin B12.[30]

The improvement of cr.cl in the intervention group from a baseline to after 72 hours of vitamin and trace element supplementation is the study's shining highlight (P-value = 0.007) while Cr.cl of the control group at a baseline to after 72 hrs. of vitamins and trace elements supplementation showed statistically insignificant change (P-value = 0.055) and when comparing the Cr.cl of the two groups after 72hr it

has to approach statistical significant (P-value=0.054), which is a shiny point in the interventional group's improvement in kidney function over the control group's improvement.

5. CONCLUSIONS

Supplementation of vitamins and trace elements in septic pediatric patients should be considered a crucial component of intensive care unit (ICU) care as they may improve creatinine clearance, and nephrotoxic drug leveling is mandatory to reduce the risk of AKI.

Recommendations:

Further studies using fat-soluble vitamins and enrolling pediatric patients who do not use the nephrotoxic drug in their empirical treatment regimen to assess the effect on another renal function. Additional clinical trials of septic pediatrics and monitoring them for more than 72 hours are needed. Additional clinical trials on a bigger sample size of septic pediatrics are needed.

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Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper (no conflicts of interest).

Ethical statement: The protocol was authorized under the rules of the Faculty of Pharmacy (Girls), Al Azhar University, Cairo, Egypt, and authorized by the Faculty of Medicine Ethical Committee, Cairo University, Cairo, Egypt (code: S-24-2019) on 12/2/2020.

Author Contribution: The following authors confirm their participation in the article: Zeinab Alkasaby, Heba Elgebaly, and Amira Fathi Anwar all helped in conceptualize and design the research; Mohamed Mostafa did formal analysis and analyze the results. Zeinab Alkasaby and Heba Elgebaly guided every step of the study.The data were evaluated and interpreted by Maha Abdelrahman and Heba Elgebaly. Mona Mohiedden supervised the laboratory techniques. Amira Fathi Anwar performed the experiment, wrote the article, conducted the experimental research with the assistance of all authors, and created the written work. And the complete version of the manuscript was agreed upon by all.

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