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Original Article

The Effect of Vitamin D3 on Serum Creatine Phosphokinase Level in Patients with Multiple Trauma: A Pilot Randomized Clinical Trial

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Abstract

Background: Multiple trauma can cause an increase in creatine phosphokinase (CPK) and subsequently rhabdomyolysis and acute kidney injury (AKI). This study was designed to evaluate the effect of vitamin D3 on the serum CPK level and the incidence of rhabdomyolysis-induced AKI in patients with multiple trauma.

Methods: Patients with serum CPK levels <1000 IU/L were followed as the control 1 group. Subjects with serum CPK levels ≥1000 IU/L were randomly allocated to the control 2 or intervention group at Imam Hossein Medical Center, Tehran, Iran in 2020. Patients in the intervention group received a single dose of vitamin D3 (300,000 units) on the recruitment day. The serum level of CPK was recorded every 3 days for 14 days. Parametric and non-parametric tests were used to compare the CPK values between groups.

Results: Forty-six patients, consisting of 16, 15, and 15 in control 1, control 2, and intervention arms of the study were recruited, respectively. Unlike control groups, the significant steadily decreasing trend was seen only in the intervention group (P<0.001). This significant decrease in the intervention arm was observed on days 5 to 7 (P=0.001) and on days 8 to 10 (P<0.001) compared to the baseline.

Patients in the intervention group had a lower number of AKI or need for dialysis (P=0.869 and P=0.670 for AKI and dialysis, respectively) than control group 2, although the differences were not significant.

Conclusion: The current study revealed that vitamin D3, could prevent the increasing trend of CPK during the first days and accelerate the normalization of CPK in patients with elevated CPK due to multiple trauma.

Trial registration number: IRCT20120703010178N23.

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Keywords ● Acute kidney injury ● Multiple trauma ● Rhabdomyolysis ● Cholecalciferol ● Creatine kinase

What's Known

- The anti-inflammatory effects of vitamin D3 and nephroprotective effects work by reducing proteinuria, preserving the glomerular structure, decreasing renal fibrosis, and inhibiting cell proliferation injury.

What's New

- Administration of vitamin D3 in patients with elevated CPK due to multiple trauma could prevent the increasing trend of CPK during the first days of trauma and accelerate the normalization of CPK in this population.

Introduction

Multiple trauma is defined as a state of physical injury where a person experiences more than one injury at a time, such as multiple bone fractures, deep wounds, and damage to internal organs such as the liver, spleen, kidneys, and so on.[1]

Overall, multiple trauma is the fourth cause of mortality worldwide. The Centers for Disease Control and Prevention reports more than five million trauma cases per year in the United States, and approximately 30% will need intensive care unit (ICU) admission due to the injury.[2] Studies showed that in general, patients admitted to the ICU due to multiple trauma show a significant increase in tissue oxidative stress levels.[3, 4] Therefore, antioxidants are expected to be an appropriate therapeutic approach in these circumstances.[5] Another complication of critically ill multiple trauma patients is elevated serum creatine phosphokinase (CPK) and rhabdomyolysis due to rapid or extensive skeletal muscle damage.[6, 7] In 30 to 55% of patients, rhabdomyolysis can lead to a serious renal complication, named acute kidney injury (AKI). In multiple trauma patients, CPK is the surrogate for rhabdomyolysis, and elevated CPK levels are correlated with a higher risk of AKI.[8]

AKI can be due to a variety of mechanisms, including systematic inflammation and oxidative stress. In this regard, substances with anti-inflammatory and anti-oxidant effects are considered potential preventive or therapeutic options.[9, 10] Among such compounds, vitamin D3 with anti-inflammatory and antioxidant properties is of interest.[11] This vitamin has been shown to play an important role in modulating inflammatory diseases such as type II diabetes, asthma, atherosclerosis, and autoimmune diseases in both clinical and molecular studies.[12]

The anti-inflammatory effects of vitamin D3 are caused by various mechanisms, including regulating pro-inflammatory cytokines, inhibiting the activation pathway of NF-κβ factor, and inhibiting inflammatory cells (macrophages, B and T lymphocytes) and prostaglandins (PG).[13, 14] Additionally, it has been proven that vitamin D3 and its analogs could have nephroprotective effects by reducing proteinuria, preserving the glomerular structure, modulating transforming growth factor beta-1 (TGF-β1) levels, decreasing renal fibrosis, and inhibiting cell proliferation injury.[15, 16] In addition, studies suggest that this vitamin could demonstrate nephroprotective effects by regulating various known pathways involved in renal injury, including the renin-angiotensin-aldosterone system (RAAS), nuclear factor-κB (NF-κB), growth factor-β (TGF-β)/Smad, and the Wnt/β-catenin signaling pathways.[17]

In the current study, we aimed to evaluate the effect of a single-dose vitamin D3 injection on the CPK levels of patients with multiple trauma. As a secondary objective, we evaluated the incidence of AKI based on AKIN criteria.[18]

Patients and Methods

Settings

The present prospective open-label randomized clinical trial (RCT) was performed between March 2019 and May 2020 in the ICU of Imam Hossein Medical Center, affiliated with Shahid Beheshti University of Medical Sciences (SBMU) in Tehran, Iran. The study has been approved by the Institutional Review Boards of the Ethics Committee of SBMU (IR.SBMU.PHARMACY.REC.1397.068). Moreover, the protocol of the study was registered, reviewed, and approved by the Iranian Registry of Clinical Trials (IRCT) (IRCT20120703010178N23). The study was conducted based on the declaration of Helsinki, and written informed consent was required for enrolment.

Study Population

Multiple trauma patients with two or more significant traumatic injuries and a total injury severity score of greater than 15, or an abbreviated injury scale >2 were evaluated based on the defined inclusion and exclusion criteria. The inclusion criteria included patients older than 18 years with at least two injuries that were diagnosed as multiple trauma by the relevant healthcare professional. Patients with characteristics including pregnancy or breastfeeding, direct trauma to the kidney, vitamin D3 serum level above 30 ng/mL, vitamin D3 consumption above 2000 IU per day in the week before the accident, history of myocardial infarction within one week before admission, phosphate level above 6 mg/dL and calcium level above 9 mg/dL at the time of admission, patients with a history of diseases related to vitamin D3 levels, such as metabolic bone disease, hyperparathyroidism, and history of organ transplantation or long-term use of immunosuppressive drugs were not included in the study.

Interventions

Serum CPK levels were measured during the first 48 hours after ICU admission. Afterward, based on the serum CPK level, patients with serum CPK levels less than five times the upper normal value (<1000 IU/L) were followed as the control 1 group. Patients with serum CPK levels equal to or greater than five times normal (≥1000 IU/L) were considered as control group 2. These patients were randomly allocated in a 1:1:1 ratio to the control groups 1, 2, or the intervention group. Randomization was done by the simple randomization method using a series of random numbers generated with the RND function of

Excel software (Microsoft Office 2016). Patients in the intervention group received a single dose of 300,000 units of vitamin D3 (Daroupakhsh Pharmaceutical Company, Iran) by intramuscular injection on the recruitment day.[19]

Assessments

For all patients, the variables consist of age, sex, cause of trauma, baseline serum 25-OH vitamin D3, and serum creatinine (Scr) concentrations. Acute Physiologic and Chronic Health Evaluation (APACHE) II score, daily urine output, and ICU length of stay were recorded by using the researcher-made checklist.[20]

Moreover, the serum level of CPK was monitored and recorded every 3 days for 14 days except for patients who were transferred to the ward or expired during the study period. For patients whose CPK did not decrease to less than 1000 IU/L, they were followed until it decreased to less than 1000 IU/L.

In this study, AKI was assessed by the AKIN criteria. According to this criteria, AKI was defined as an 0.3 mg/dL or more increase in the Scr levels or increasing Scr concentration to more than 1.5 fold of its baseline value within 48 hours or a decrease in the urinary output to less than 0.5 mL/kg/h for more than 6 hours.[19]

Sample Size

As this is the first human study on this issue, we did not calculate the sample size, and we designed this study as a pilot and considered 15 patients in each group based on expert opinion.

Statistical Analysis

Data were analyzed according to the initial group allocation (intention to treat). Quantitative data were assessed for normality of distributions by the Shapiro-Wilk test and Q-Q plot. The data are presented as mean±standard deviation (SD) or frequency and percentage (%).

Three groups were compared by One-way ANOVA or Kruskal-Wallis tests for normal and non-normal distribution data, respectively. Besides, the *post hoc* analysis (Dunn's test) was performed for the CPK level at baseline to identify exactly which groups differ from each other.

The student's *t* test or Mann-Whitney U test for normal and non-normal distribution data, respectively, were used when the comparison between the two groups was the goal. The distribution of categorical data was compared by the Chi square or Fisher's exact test. A Spearman's rank correlation test was used to assess the correlation between variables.

For comparison of the mean serum CPK levels between two different times, a paired *t* test or Wilcoxon rank-sum test was used.

A linear Generalized Estimating Equation (GEE) with an exchangeable correlation structure was considered as the repeated measurements to assess the changes in CPK during the study time. The Bonferroni correction for the level of significance was applied to each time comparison. On the other hand, for this correction, the initial level of significance (α=0.05) was divided by the number of comparisons (n=6). Therefore, instead of using 0.05 as the critical level of significance for comparing times, we used P<0.008 (0.05/6=0.008).

In addition, the Kaplan-Meier plotter was used to show the effect of vitamin D3 therapy on decreasing the CPK level <1000 IU/L during hospitalization. The P value for comparison of time to event curves between groups was determined by log-rank test. All of the statistical analysis was set as P<0.05 and was carried out using STATA version 14 (StataCorp LLC, College Station, TX 77845, USA).

Results

Baseline Data

In total, 83 patients with multiple trauma were assessed, of which 37 were not included (figure 1). Eligible patients included 11 females and 35 males, of which 16 were in control group 1 with CPK<1000 (mean age 58.50±25.13 years), 15 in control group 2 with CPK>1000 (mean age 49.67±22.25 years), and 15 in the intervention group (mean age 45.60±15.70 years). Hypertension (N=16, 34.78%), diabetes (N=15, 32.61%), and a history of myocardial infarction (N=5, 10.87%) were the prevalent underlying diseases, respectively.

Comparing the baseline characteristics of patients revealed that there were no significant differences in gender, cause of trauma, urine output, APACHE II score, baseline serum creatinine, and baseline vitamin D3 level among the three groups. Only a statistically significant difference was observed in the prevalence of hypertension among study groups (P=0.036) (table 1). Furthermore, there was a statistically significant difference between baseline CPK values between groups (P=0.002) (table 1). More analysis revealed that this difference in mean CPK level was statistically significant in control group 1 compared to the control group 2 (P=0.001) and the control group 1 with the intervention group (P=0.004), and there was no statistically significant difference in the baseline CPK level of the control 2 and intervention arms of the study (P=0.724).

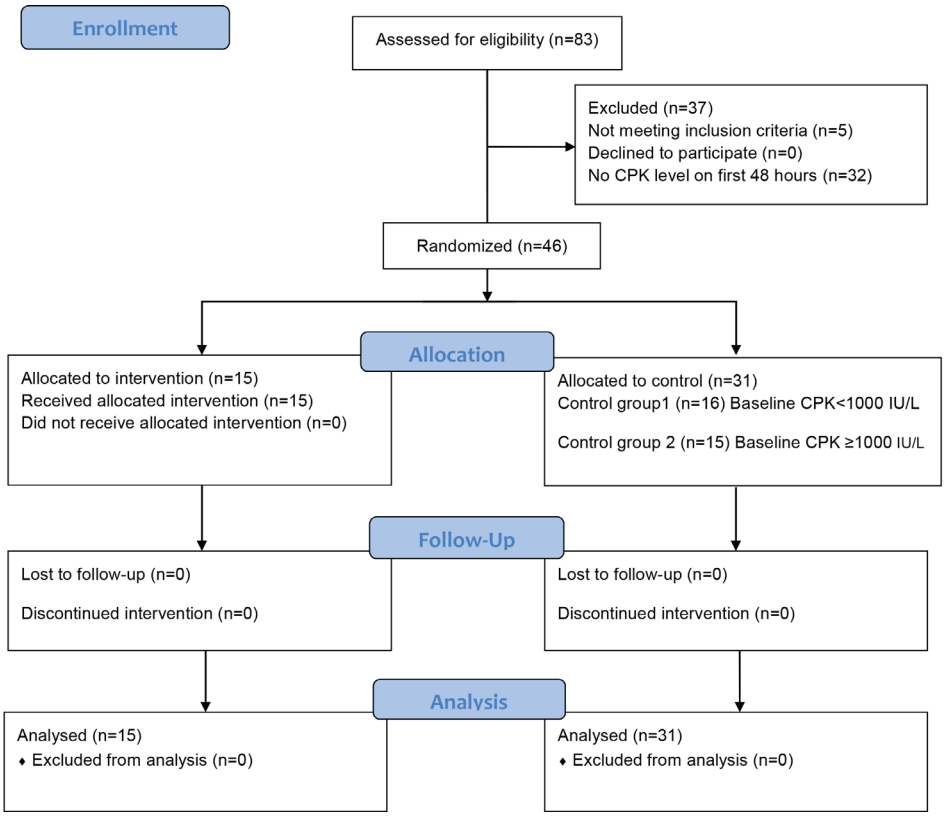

Figure 1: The figure represents the CONSORT flow diagram of the study.

Table 1: Baseline characteristics of under-study patients

Variables		Total (N=46)	Control group 1 (N=16)	Control group 2 (N=15)	Intervention (N=15)	P value
Age (years)		51.41±21.71	58.50±25.13	49.67±22.25	45.60±15.70	0.389
Sex	Male	35 (76.09)	10 (62.50)	13 (86.67)	12 (80.0)	0.316
	Female	11 (23.91)	6 (37.50)	2 (13.33)	3 (20.0)	
Hypertension	Yes	16 (34.78)	9 (56.25)	5 (33.33)	2 (13.33)	0.036[a]
	No	30 (65.22)	7 (43.75)	10 (66.67)	13 (86.67)	
Diabetes	Yes	15 (32.61)	7 (43.75)	4 (26.67)	4 (26.67)	0.571
	No	31 (67.39)	9 (56.25)	11 (73.33)	11 (73.33)	
Myocardial infarction	Yes	5 (10.87)	2 (12.50)	3 (20.0)	0 (0.0)	0.259
	No	41(89.13)	14 (87.50)	12 (80.0)	15 (100.0)	
Causes of trauma	Car accident	21 (45.65)	7 (43.75)	7 (46.67)	7 (46.67)	0.230
	Motorcycle accident	12 (26.09)	3 (18.75)	2 (13.33)	7 (46.67)	
	Fall	10 (21.74)	4 (25.0)	5 (33.33)	1 (6.67)	
	Others**	3 (6.52)	2 (12.50)	1 (6.67)	0 (0)	
ICU stay (days)		27.89±14.91	28.69±18.60	28.60±11.61	26.33±14.33	0.846
APACHE II		16.22±7.19	17.81±5.29	16.64±8.49	14.13±7.61	0.359
Creatine phosphokinase (CPK, IU/L)		2218.57±2335.01	179.5±194.56	2519.78±1435.93	3805.83±3208.78	0.002[b]
Serum creatinine (mg/dL)		2.03±2.50	1.70±1.10	2.02±1.49	1.37±0.63	0.281
Vitamin D3 (IU)		16.009±10.64	20.66±13.78	15.62±9.66	11.32±4.91	0.323
Urine output(mL/day)		2006.25±1022.33	2204±989	1658±947	2146±1106	0.331

Data presented as frequency (%) or mean±SD; P values were estimated based on one-way ANOVA or Kruskal-Wallis tests for comparing means and Chi square or Fisher's exact tests for comparing frequencies. [a]Significant based on Fisher's exact test; [b]Significant based on the Kruskal-Wallis test; **Such as suicide, violence, and objectives fall

Serum CPK Level

Changes and Within-Group Comparison: As shown in figure 2, based on linear GEE results, a declining trend of serum CPK levels was observed in all groups during the study period (P=0.019). Changes in CPK in control group 1 were statistically significant (P<0.001). Changes in CPK in control group 2 were not statistically significant (P=0.319). The steadily significant decreasing trend was seen only in

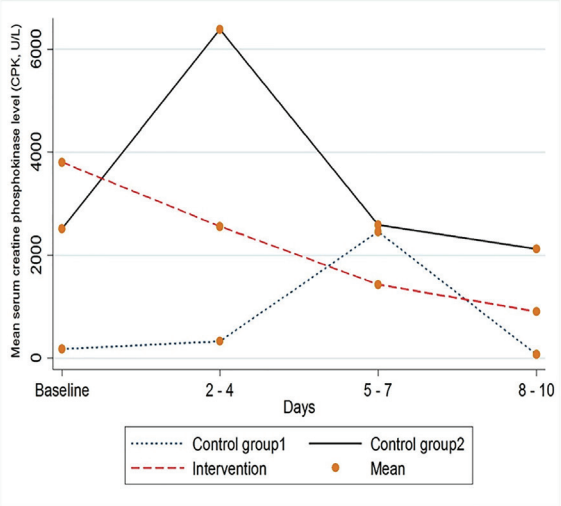

Figure 2: Changes in the mean of serum creatine phosphokinase level (CPK) between three groups during study time.

the intervention group (P<0.001). In addition, a significant interaction effect between time and groups was observed (P<0.001).

A multiple comparison following a significant trend of CPK levels in the intervention and control group 1, with a corrected level of significance based on the Bonferroni correction (P<0.008), was applied. Based on the results, it was observed that in control group 1, the increase in the mean CPK level from days 5 to 7 (P=0.031) and the CPK changes from days 8 to 10 (P=0.024) compared to the baseline was not statistically significant. However, a significant decrease in the intervention arm was observed on days 5 to 7 (P=0.001) and days 8 to 10 (P<0.001) compared to the baseline.

Additionally, the changes in CPK levels at days 2 to 4 compared to the baseline were not significant in the intervention arm (P=0.399) and control group 1 (P=0.162).

Further analysis showed that the changes in CPK levels at days 5 to 7 and 8 to 10 compared to days 2 to 4, as well as days 5 to 7 compared to 8 to 10, were not statistically significant in the intervention and control group 1 (P>0.008, corrected level of significance).

Between Groups Comparison: On the second measurement of the CPK at days, 2 to 4, the serum level of CPK increased in control groups 1 and 2 and decreased in the intervention group compared to the baseline, and a significant difference in mean CPK was observed between the three arms at days 2 to 4 (P<0.001). Further analysis showed that the difference in mean CPK levels between control group 2 and intervention group at days, 2 to 4, was not statistically significant (P=0.068). At this time, the serum level of CPK was significantly higher in the intervention arm of the study compared to the control group 1 (2559.32±1807.5 *vs.* 328.16±292.82 IU/L, P<0.001) on the second measurement. This difference was also significant between control 1 and 2 arms of the study (328.16±292.82 *vs.* 6383±7708.74, P<0.001). The differences between CPK levels on days 5 to 7 and on days 8 to 10 measurements were not significant among study groups (P=0.650 and P=0.277, respectively) (figure 2).

Furthermore, we followed the subjects in control group 2 and the intervention arm of the study regarding the time to decrease CPK to less than 1000 IU/L. Based on the Kaplan-Meier estimation, the CPK levels decreased to less than 1000 IU/L faster in the intervention group than in the control 2 arm of the study. Although, the difference between these groups was not statically significant (P=0.127) (figure 3).

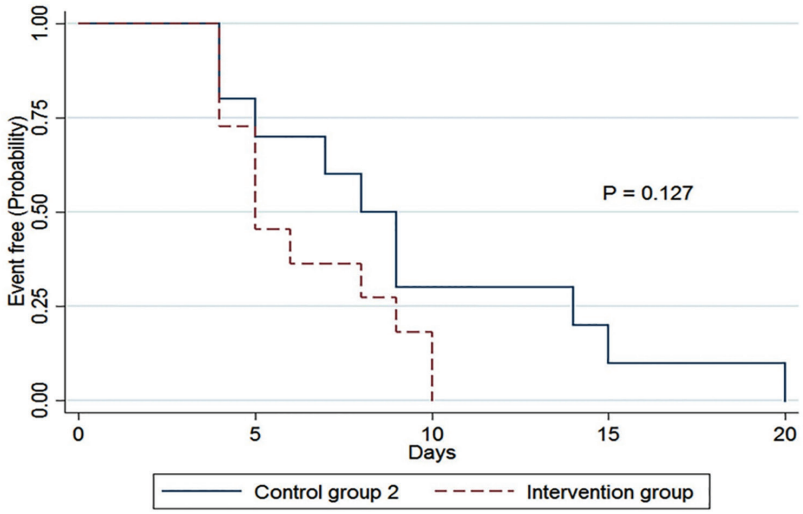

Figure 3: Kaplan-Meier curve for time to event (serum creatine phosphokinase level (CPK)<1000 U/L) analysis in intervention and control group 2.

Table 2: The incidence of AKI and the need for dialysis during hospitalization

Variables		Total (N=46)	Control group 1 (N=16)	Control group 2 (N=15)	Intervention (N=15)	P value
Acute Kidney Injury (AKI)	Yes	17 (37.78)	6 (37.50)	6 (40.00)	5 (33.33)	0.869
	No	28 (622.22)	10 (62.50)	9 (60.00)	10 (66.67)	
Dialysis	Yes	7 (15.22)	3 (18.75)	3 (20.0)	1 (6.67)	0.670
	No	39 (84.78)	13 (81.25)	12 (80.0)	14 (93.33)	

Data are presented as frequency (%); P values were estimated based on Chi square or Fisher's exact tests.

Table 3: Baseline characteristics of patients with and without experience of AKI during hospitalization

Variables	With AKI (N=17)	Without AKI (N=28)	Total (N=45)	P value
APACHE II score	19.52±7.62	14.21±6.22	16.22±7.19	0.014[a]
Basal creatinine level (mg/dL)	3.28±3.82	1.31±0.65	2.02±2.50	<0.001[b]
Basal CPK (IU/L)	2144.80±2549.16	2402.60±2332.20	2218.57±2335.01	0.650
Basal vitamin D3 (I.U)	21.14±13.01	12.48±7.26	16.009±10.64	0.065
Urine output(mL/Day)	1220.58±630.98	2640±835.75	2006.25±1022.33	<0.001[b]
History of hypertension (yes)	9 (52.94)	6 (21.43)	15 (33.33)	0.030[c]
History of myocardial infarction (yes)	1 (5.88)	3 (10.71)	4 (8.89)	0.511
History of diabetes (yes)	7 (41.18)	7 (25.00)	14 (31.11)	0.256

Data are presented as frequency (%) or mean±SD; P values were estimated based on student's *t* test or Mann-Whitney U test for comparing means and Chi square or Fisher's exact tests for comparing frequencies; [a]Significant based on the student's t test; [b]Significant based on the Mann-Whitney U test; [c]Significant based on Chi square's test

Occurrence of AKI

The incidence of AKI and the need for dialysis were assessed in the three groups during the study period. Although the number of patients who developed AKI or needed dialysis was lower in the intervention group, this difference was not statistically significant (P=0.869 and P=0.670 for AKI and dialysis, respectively) (table 2).

Moreover, baseline data between patients with and without AKI were assessed regardless of their group, and data are shown in table 3. According to the results, among patients with AKI, the APACHE II score (P=0.014), and basal creatinine level (P<0.001) were higher, while the mean of urine output (P<0.001) was lower in patients with AKI than in other patients. There was no statistically significant difference in the baseline serum levels of CPK and serum 25-OH vitamin D3 between patients with and without AKI.

Additionally, we evaluated the relationship between the baseline serum level of CPK, before administration of vitamin D3, and baseline serum 25-OH vitamin D3 concentration. There was no significant correlation between the two variables (spearman's correlation (r)=-0.12, P=0.640). Although the mean of the baseline serum 25-OH vitamin D3 concentration was higher in control group 1, which had CPK levels below 1000 IU/L, there was no statistically significant difference between the three groups (P=0.323).

Discussion

Our results revealed a significant decrease in the CPK levels, besides faster normalization of CPK levels with a single dose of vitamin D3 administration during the first days after trauma. Besides, the incidence of AKI and renal replacement therapy was lower in the intervention group, but it was not statistically significant.

In the study by Assanangkornchai and colleagues, the authors revealed that CPK levels increase during the first 72 hours in multiple trauma patients,[21] which is in accordance with our findings in control groups 1 and 2; but interestingly, the group received vitamin D3, and the serum CPK levels decreased. This finding supports that the administration of vitamin D3 could prevent the increasing pattern of CPK during the first days after trauma.

The occurrence of rhabdomyolysis was reported in severe exertion in patients with vitamin D3 deficiency.[22, 23] A possible explanation for this might be that vitamin D3 can improve muscle strength and plays an important role in the normal function of muscles.[24, 25] Furthermore, a relationship between vitamin D3 deficiency and AKI has been reported in the literature.[26, 27] It is suggested that vitamin D3 disorder can lead to the development of AKI, while also, AKI can contribute to dysregulation of homeostasis and function of vitamin D3, therefore vitamin D3 is suggested to be an important therapeutic option for AKI.[26]

In our study, it was also seen that the administration of high-dose vitamin D3 reduced the incidence of AKI and the subsequent need for dialysis in multiple trauma patients, although this reduction was not statistically significant, which

requires further study with a larger sample size.

Critically ill patients with multiple trauma commonly experience oxidative stress immediately after the initial trauma. Oxidative stress and necroinflammation could persuade rhabdomyolysis-induced AKI, which contributes to high morbidity and mortality.[3, 6] Therefore the use of antioxidant therapies such as vitamin C, vitamin E, and N-acetyl cysteine was investigated in multiple trauma patients to decrease complications such as rhabdomyolysis-induced AKI, mortality rate, and ICU length of stay.[28]

Overall, because of the relationship between vitamin D3 and rhabdomyolysis and AKI, and since vitamin D3 has proven antioxidant and nephroprotective effects,[11] it can be a promising medication for preventing the occurrence of rhabdomyolysis and AKI. Until now, based on our research, there was no study to evaluate the effect of vitamin D3 on the incidence of rhabdomyolysis and AKI-induced rhabdomyolysis, so we designed this pilot study. Only an animal study examined the effect of calcitriol, an active metabolite of vitamin D3, in the AKI induced by rhabdomyolysis, which showed a promising role of calcitriol in decreasing oxidative damage and inflammation in the animal model.[29]

Another outcome of the current study was the faster normalization of the CPK in the intervention group, which did not reach a significant level. A possible explanation for this might be that the current study was a pilot study, and the time to normalization of the CPK was defined as a secondary objective in the current study.

Conclusion

The current study revealed that administration of a single 300,000 unit vitamin D3 in patients with elevated CPK due to multiple trauma, could prevent the increasing trend of CPK during the first days of trauma and accelerate the normalization of CPK in this population. Despite the lower number of subjects who needed dialysis in the group receiving vitamin D3, this difference did not reach a significant level, which may be due to the small sample size.
Studies with a higher sample size in the form of double-blind and placebo control can show this significant difference.

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Authors' Contribution

M.K: Conceptualization, resource acquisition, project administration, and review of the final manuscript; N.T: analysis and interpretation of data for the work, revising and reviewing the final version; M.F: Interpretation of data and drafting the work; M.M: Conceptualization and review the final manuscript; S.S: acquisition of data and drafting the manuscript; S.Sh acquisition of data and review the final manuscript; R.H: Writing original draft and interpretation of data; H.A: acquisition of data, review and response to editor and resubmission; M.S: Conceptualization, reviewing final version. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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