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Comparison of Mortality in Critically ill Children Admitted to the Intensive Care Unit with and without Vitamin D Treatment

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A B S T R A C T

Vitamin D holds various roles in body from Calcium homeostasis to modulating immune system. Though, different studies have shown high prevalence of vitamin D deficiency in ill patients, there is lack of one clinical trial that shows the effect of repleting this deficiency and its clinical outcomes. So, the purpose of this study is to compare the mortality of the hospitalized patients in PICU (Pediatrics Intensive Care Unit) in groups with and without the treatment with vitamin D. One-hundred-and-one hospitalized patients in the PICU of children's hospital in Tabriz during the year (2013-2014) with vitamin D deficiency were considered as the intervention group receiving vitamin D. Also 101 patients were chosen for control group, after equalizing the risk factors by the PRISM III and SOFA scores with intervention group. Calcium and Phosphorus amounts were measured in the very first moments of their hospitalization. Vitamin D was administered 300000 IU intramuscular for the intervention group after measurement of vitamin D level, and the level of vitamin D, duration of hospitalization in hospital and PICU, the duration of being under ventilator and the need for vasopressors agent during hospitalization was measured. The duration of hospitalization in hospital (p<0.001) and PICU (p<0.001), the duration of being under mechanical ventilation (p=0.014) and the need for vasopressors agent (p=0.003) were significantly higher in control group. Also the mortality was significantly higher in intervention group (p<0.001). Vitamin D levels oscillations in expired and discharged patients in intervention group, both were significantly lower in expired patients (p<0.001). This study showed that patients with vitamin D deficiency in PICU have higher rates of mortality in comparison to patients with normal ranges of vitamin D. Also, patients with vitamin D deficiency who expired during their hospitalization did not have sufficient increase in vitamin D levels despite receiving vitamin D supplements.

Introduction

Vitamin D is a vital vitamin for body growth. It is the only vitamin that functions as a hormone in body and regulates the distribution of 200 genes.

In addition to its known role in the metabolism of calcium, it activates cell growth regulatory genes and contributes to the production of immunomodulator. There

is ample evidence that signifies the effect of vitamin D on inflammatory cytokines, T-cells, and immune responses. Numerous studies in recent years have demonstrated the significance of vitamin D in maintaining musculoskeletal health. The concurrence of chronic diseases with vitamin D deficiency shows the vital role this vitamin plays in critically ill patients. According to these studies, changes in vitamin D levels and its metabolites are common in critically ill patients; yet, it is not yet known whether vitamin D deficiency exacerbates underlying conditions or it is the other way around. Moreover, it is yet to be understood whether replacing vitamin D is effective in the improvement of critically ill patient prognoses (1-2).

It was revealed in a study that a lower-than-20 ng/ml vitamin D serum level had significant impacts on length of stay (LOS), organ dysfunction rates, and infection levels (3).

In the study conducted by Morandi (2013) on a cohort of 120 Pediatric Intensive Care Unit (PICU) patients, low serum 25-(OH)D was associated with delirium (4).

In another study conducted by Granados (2010) on PICU patients, they exhibited vitamin D deficiencies (5).

Despite a lack of consensus over vitamin D deficiency mechanism of action in critically ill patients, many medical centers around the world have recently begun to address this issue in critically ill patients due to the substantiated significance of overcoming such deficiency in treating children. Since Tabriz Children's Hospital provides service to patients in northwestern Iran and on account of a lack of vitamin D serum level measurement at its PICU for the moment, the present study sought to compare the

mortality rate of Tabriz Children's Hospital PICU patients with/without vitamin D treatment.

The aim of this study was to compare the mortality rate of Tabriz Children's Hospital PICU patients in two with and without vitamin D treatment groups.

Materials and Methods

In a clinical trial conducted on PICU patients in Tabriz, their mortality rates in two group of with and without vitamin D treatment were investigated. The intervention and control groups of this study consisted respectively of 101 and 100 PICU patients hospitalized at the Tabriz Children's Hospital with and without vitamin D deficiencies based on the performed tests.

Inclusion Criteria

Longer-than-24 hour hospitalizations

Parental consents

Exclusion Criteria

Patients who passed away within the first 24 hours of admission

Patients who were transferred to other units within the first 24 hours of admission

A lack of consent on the part of patients' legal guardians

Patients with a history of hypercalcemia or nephroliths

The present study was a clinical trial conducted in 2014 in which 101 and 100 PICU patients hospitalized at the Tabriz Children's Hospital with and without vitamin D deficiencies were respectively

selected as the intervention and control groups using the random sampling method. Written informed consents were obtained from the patients' parents. Diagnostic and therapeutic measures were taken based on what was deemed necessary to do according to PICU procedures. In addition to daily routine checks conducted on all patients, blood samples were collected intravenously at the baseline and seven days following treatment and were transferred to Danesh Pathobiology Center in Tabriz on the same days they were taken in order to measure 25-(OH)D serum levels by chemiluminescent techniques. Vitamin D deficient patients were then treated with vitamin D (300000 IU/im vitamin D3) by the researcher using STOSS therapy. Patients underwent follow-up tests and their relevant data were collected based on data collection forms until the end of treatment and reaching a final outcome (discharge or demise). Patients who did not suffer from vitamin D deficiency were regarded as the control group. PRISM III and SOFA scores were utilized to determine the severity of disease in vitamin D deficient/sufficient patients. On account of the advice from the University Ethics Committee and the potential role of vitamin D deficiency in increasing mortality rates, we were not ethically allowed to divide vitamin D deficient patients to two treatment and placebo receiving groups, making us obliged to treat all patients. Furthermore, due to the potential impact of vitamin D prescription on mortality and morbidity rates, it was not possible to divide the patients to two placebo receiving and vitamin D deficient groups to compare mortality rates and other variables between vitamin D deficient/sufficient groups after the initiation of treatment. Changes in vitamin D levels were then measures in intervention and control groups and their relationship with mortality rates were investigated. Written informed consents were obtained from patients' parents or legal guardians and no change was made in patients' diagnostic or therapeutic procedures. The obtained information will remain confidential.

Statistical Analysis

Descriptive methods (frequency, percentage, mean ± SD) were used for statistical analysis and the chi-square test (X2) and mean difference test were used to compare. All statistical analyzes were performed with SPSS 17 statistical software. The p<0.05 was considered significant in all cases.

Results and Discussion

101 PICU vitamin D deficient patients were matched and compared with 100 PICU vitamin D sufficient patients in terms of PRISM III and SOFA scores. The mean PRISM III score in the intervention and control groups was 34.24 and 48.24, respectively. The mean SOFA score was 39.3 for both groups.

The mean age of intervention and control groups was 45.85± 51.4 and 48.78 ± 41.76 months, respectively (P = 0.992).

In terms of gender, the intervention and control groups consisted of 52 (51.5%) and 60 (59.9%) boys and 49 (48.5%) and 41 (40.1%) girls, respectively (P = 0.257).

The mean LOS at PICU for intervention and control groups was 20.6 ± 10.99 and 14.12 ± 8.14 days, respectively (P < 0.001). The mean hospital LOS for intervention and control groups was 35.13 ± 11.2 and 23.9 ± 7.7 days, respectively (P < 0.001).

Mechanical ventilation (MV) was used for all patients. The mean MV length in intervention and control groups was 251.46

± 193.15 and 195.33 ±115.89 hours, respectively; the former being significantly longer (P = 0.014).

All control group and 98% of intervention group patients were treated with a vasopressors agent. The mean length of receiving vasopressors agent for intervention and control groups was 188.77 ±111.35 and 146.15 ± 87.53 hours, respectively; the former being significantly longer (P = 0.003).

In the intervention group, 62 patients passed away, 37 were discharged with sequelae, and 2 were discharged with recovery.

In the control group, 29 patients passed away, 11 were discharged with sequelae, and 60 were discharged with recovery. The mortality rate was significantly higher in the intervention group (P < 0.001).

Vitamin D levels increased significantly less in the deceased patients 7 days following the treatment, which signifies the direct relationship between vitamin D levels and increased mortality rates among these patients (P <0.001). It is therefore concluded that vitamin D levels increased significantly less in the intervention group's deceased patients.

Results indicated that vitamin D levels were significantly lower among the deceased PICU patients compared to those who had survived (P < 0.001), which is completely in line with the findings of the studies that will be discussed shortly.

In the study conducted by Azim et al, at a tertiary referral center on the prevalence and consequence of vitamin D deficiency among 158 critically ill ICU patients, it was revealed that 80.4% of these patients were vitamin D deficient and that such deficiency was very common among gravely ill patients. It was also demonstrated that vitamin D levels among survivors were higher than the deceased; yet, no causal relationship was shown between vitamin D deficiency and mortality rate among critically ill patients. APACHE II score, blood lactate, and pre-ICU LOS were independent factors predicting mortality in these patients (6).

In a study conducted by Amrein et al, on 655 critically ill surgical and nonsurgical ICU patients, it was demonstrated that low 25-(OH)D levels were significantly related to mortality rates. Normal vitamin D levels were merely observed in 13.6% of patients. Hospital mortality rate was significantly higher in groups with low or moderate vitamin D levels. Moreover, no significant relationship was observed between 25-(OH)D, and C-reactive protein (CRP) and Procalcitonin (PCT) levels as well as white blood cell (WBC) counts (7).

In our study, mortality rate was also higher among vitamin D deficient children compared to those with normal vitamin D levels.

In the study carried out by Aygencel et al, on 201 critically ill ICU patients, vitamin D deficiency was observed in 69% of patients. Patients with inadequate vitamin D serum levels were associated with more acute illnesses and less desirable laboratory findings. In addition, the stated group suffered a higher morbidity rate in face of invasive procedures. the mortality rate was significantly higher in the vitamin D deficient group, i.e. 43% compared to 26% (P = 0.027). However, logistic regression analysis did not introduce vitamin D deficiency as an independent risk factor for mortality (8).

In the present study, the mortality rate of vitamin D deficient and sufficient children

was 62% and 29%, respectively; with the former being significantly higher.

A recent review study by Schottker et al, demonstrated that. Although vitamin D did not play a part in the development of cardiovascular diseases or cancer by itself, it could play a flexible influential role in reducing mortality in such patients (9).

Another study conducted by Madden et al, on 511 critically ill PICU patients revealed that a high percentage of these patients (40.1%) suffered from vitamin D deficiency (10). Lower vitamin D levels were related to the severity of disease at the time of hospitalization (P < 0.001). Furthermore, given the important role of vitamin D in the immune system development, the significance of screening critically ill patients and those exhibiting vitamin D deficiency risk factors as well as of prescribing vitamin D supplements for such patients has been illustrated in the aforementioned study.

In the study performed by McNally et al, on 326 critically ill patients at six PICU centers, the prevalence of vitamin D deficiency was reported as 69%. In addition, it was revealed that lower vitamin D levels were associated with hypocalcaemia, catecholamine administration, and considerable intravenous fluid intakes. Furthermore, the impact of vitamin D deficiency, as an independent factor, on predicting longer PICU stays (P = 0.03) as well as its relationship with the severity of disease determined by PRISM III scores was established (11). In the present study, PRISM III scores were also significantly higher among the deceased children (P < 0.001).

According to the obtained results, lower vitamin D levels were significantly related to the use of vasopressors agents (P = 0.003), MV (P = 0.014), and LOS (P <

0.001), significantly increasing these variables and causing additional complications. The results correspond to those of the previous studies, underlining the impact of the aforementioned variables on mortality rates.

In the study conducted by Cecchi et al, on 170 ICU patients with severe sepses, septic shocks, or major traumas, it was revealed that the vitamin D serum levels of the sepsis group were significantly lower than those of the trauma group upon admission (P < 0.001). It was also shown that the sepsis group mortality rate was significantly related to their vitamin D levels upon admission. Yet, no distinct relationship was observed between vitamin D levels and patient outcomes (12).

In another study carried out by Chen et al, on 236 ICU patients, it was demonstrated that vitamin D deficient patients upon admission received higher APACHE II and SOFA scores. In addition, they exhibited more cases of positive blood cultures, higher PCT and intact parathyroid hormone (iPTH) levels, and a higher mortality rate within the first 28 days. Among other observed parameters were lower ionized calcium levels, longer PICU stays, and longer needs for MV (13).

In the study conducted by Haghbin et al. on 294 ICU patients, the mortality rate among the low ionized calcium level group was significantly higher than its normal level counterpart (5% compared to 25%). Moreover, a significant relationship was observed between low serum calcium concentrations and high PRISM III scores and calcitonin levels. A significant relationship was also observed in terms of PRISM III scores and calcitonin and ionized calcium levels between the deceased and those who had survived. However, this relationship did not apply to parathyroid

hormone (PTH) levels and the specified variables (14). Similar to the above study, the deceased children in the present study had significantly lower ionized calcium levels compared to the survivors (P < 0.001).

In a clinical trial conducted by Amrein et al, on 475 critically ill ICU patients, the intervention group was treated with high doses of vitamin D. However, no significant

difference was seen between the LOSs of the two groups. A similar result was obtained in a study conducted on 200 patients with severe vitamin D deficiency. No significant difference was also noticed in the hospital and six-month mortality rates of the two groups. However, the hospital mortality rate was significantly (P = 0.04) lower among patients with severe vitamin D deficiency who received treatment (15).

Table.1 Studied Parameters Based on Outcome

	Death	Outcome Discharged with sequelae	Discharge with Improvement	P
Age	47.30±48.34	54.91±49.32	45.17±41.72	0.528
MV Time	258.87±129.34	213.37±233.27	179.79±125.33	0.011
Vasopresure Time	201.41±101.08	142.29±99.95	138.00±91.34	<0.001
PICU Time	22.34±11.42	15.27±7.57	11.69±5.63	<0.001
Hospital stay time	32.30±9.64	33.94±14.12	22.08±5.76	<0.001
Vit. D first day	24.31±42.95	18.30±12.29	40.46±8.08	<0.001
Vit D 7th day	20.82±5.49	31.25±6.59	33.00±0.00	<0.001
Vit. D changes	8.68±4.02	18.71±5.79	15.15±0.92	<0.001
Ca^{+2}	1.07±0.19	1.12±0.15	1.28±0.05	<0.001
P	3.90±0.55	3.92±0.54	4.61±0.35	<0.001
PRISM III	31.09±5.09	15.69±7.76	21.61±10.00	<0.001
SOFA score	3.96±0.26	2.79±0.80	3.05±0.89	<0.001

In the study carried out on two intervention groups (the deceased and the discharged), vitamin D levels increased significantly less in the deceased group despite treatment with vitamin D (P < 0.001). Considering that the highest under-five (child) mortality rate in Iran is associated with under-one (infant) mortality, the above findings underscore the importance of overcoming vitamin D deficiency in mothers and children as a potential way of reducing child mortality in the country which is one of the primary goals of the Ministry of Health and Medical Education. These findings correspond to

those of all studies conducted regarding the effect of vitamin D on reducing mortality rates.

In the present study, there was also a significant relationship between low vitamin D levels and increased mortality rates (P < 0.001).

In a retrospective study undertaken by McKinney et al, on PICU patients, it was demonstrated that the prevalence of vitamin D deficiency among the deceased was considerably higher than the survivors.

Moreover, the number of vitamin D deficient patients who had been hospitalized at PICUs for more than three days was significantly higher than children who had normal vitamin D levels (58% compared to 29%). Finally, mortality risk in vitamin D deficient ICU patients was higher (16).

In the study conducted by Higgins et al, on 196 PICU patients, 82% of then had lower-than-normal vitamin D levels. After three days of hospitalization at PICU, 25-(OH) D levels decreased in all patients (P < 0.001). No relationship was found between vitamin D levels and mortality rates after 28 days. Yet, higher vitamin D levels showed significant relationships with shorter LOSs. In addition, vitamin D deficient patients were significantly more prone to various infectious diseases (17).

In the present study, ANOVA test results revealed that, despite treatment with vitamin D, vitamin D levels increased significantly less in the deceased children compared to those who had survived among whom vitamin D increased to normal levels (P < 0.001).

This may be accounted for by the production of various antioxidants in critically ill patients with higher PRISM III scores. Further studies need to be carried out in this regard to determine the real causes. The above findings are consistent with those of Higgins et al. (2012).

Comparing 156 PICU patients with 289 healthy children, Rey et al, demonstrated that PICU patients' vitamin D levels were significantly lower (P < 0.007).

In general, hypervitaminosis D was significantly higher in PICU patients. Moreover, it was illustrated that vitamin D level did not have a significant relationship with increased mortality risk (18). The present study points to the existence of a significant relationship between vitamin D levels and hospital LOSs (P = 0.014) as well as PICU LOSs (P < 0.001).

Furthermore, it was shown that PICU vitamin D deficient children developed more complications than those whose vitamin D levels were normal, which could significantly lead to increased child mortality rates. Despite receiving vitamin D supplements, vitamin D deficient patients who eventually passed away during hospitalization did not exhibit adequate serum vitamin D level increases.

Increased vitamin D levels during treatment were also shown to have a significantly negative relationship with child mortality rates. The present study aimed at investigating the effects of vitamin d supplement prescriptions on the improvement of PICU vitamin D deficient patients' clinical conditions.

In conclusion, by dividing PICU vitamin D deficient critically ill patients to two intervention and control groups, future studies can investigate the effects of vitamin D supplement prescriptions on the stated groups and provide more detailed results with regards to its effectiveness. Increasing the number of patients as well as conducting prospective cohort studies at medical centers with differing epidemiological characteristics could yield more reliable results. Given the significant role of vitamin D on critically ill PICU patients, it is recommended that vitamin D serum levels be measured for all admitted children as a general guideline. The findings of this thesis can have practical applications in reducing child mortality and promoting children's health which are in line with the defined objectives by the Iranian Ministry of Health and Medical Education.

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