Original Research Article

Correlation of serum creatine phosphokinase and serum cholinesterase in organophosphate poisoning in children

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ABSTRACT

Background: Organophosphate (OP) poisoning is one of the most common pesticide poisoning in India in adolescents because of its easy availability. Serum pseudocholinesterase levels are commonly used to assess the severity and to know the prognosis in OP compound poisoning. Serum creatine phosphokinase (CPK) levels is another lab parameter which gets deranged in OP poisoning and has been tried in adults to assess the severity and to know the prognosis.

Authors objective was to study the correlation of serum pseudocholinesterase and serum CPK in organophosphate poisoning at admission and to compare outcome with serum CPK levels.

Methods: All the children in the age group of 1 month to 18 yrs, who were admitted with the history of suspected OP compound poisoning were enrolled for the study. Estimation of cholinesterase and CPK levels were done at admission and after 1 week. Patients were categorised in to latent, mild, moderate and severe cases based on the S. Cholinesterase levels. These values were analysed to see the correlation.

Results: Among 34 OP poisoning cases,13(38%) were males and 21(62%) were females. Mean age of study population was 12.6±4.25 yrs. The median CPK values in latent, mild, moderate and severe cases were 121.5 IU/L, 276.5 IU/L, 308IU/L and 467IU/L respectively (p=0.015). Spearman’s rho Correlation coefficient was -0.522 between S. Cholinesterase and S CPK at admission which was significant. The median serum CPK level after 1 week in non survivors was 2498.0IU/L and in survivors was 201.0IU/L (p=0.014).

Conclusions: There was a strong negative relationship between serum cholinesterase and serum CPK at admission in OP poisoning. Follow up values at 1 week showed that significantly high serum CPK and low cholinesterase, which was also significant and was associated with mortality.

Keywords: Correlation, Mild poisoning, Moderate poisoning, Organophosphate poisoning, Serum creatine phosphokinase, Serum Pseudocholinesterase, Severe poisoning

INTRODUCTION

Organophosphate (OP) poisoning is a major health issue worldwide especially in agricultural countries like India and Srilanka. The WHO estimates that approximately 3 million pesticide poisoning occurs worldwide and causes more than 220,000 deaths. Suicidal and occupational OP poisoning in agricultural workers is prevalent in developing countries. Children accounted for 35% of the OP-poisoned victims. In our college, OP poisoning accounted for 0.5% of hospital admissions in paediatric department during the study period.

Organophosphates produce toxicity by binding to and inhibiting the acetyl cholinesterase enzyme (AchE) preventing the degradation of acetylcholine resulting in its accumulation at nerve synapses, producing muscarinic and nicotinic receptors over activity. The clinical
manifestation begin within 1/2 to 1 hour and reach peak in 2 to 8 hours. Signs and symptoms appear when the cholinesterase activity drops to 50% of its normal.

Usual investigations include serum erythrocyte cholinesterase (EchE) and plasma cholinesterase (PchE) estimation. When RBC cholinesterase better reflects the synaptic inhibition, serum cholinesterase levels declines fast and assessment is easy. Some other blood parameters also gets deranged in OP poisoning, which is supportive in severity assessment and prognostication, such markers are being tried recently, one among which is muscle injury parameter, S.CPK.

Sahjian et al, showed serum CPK normalizes within 5-6 days of a single insult to the muscle and when there is ongoing muscle injury due to development of complications, the CPK level continues to be elevated.4

It was proved in some studies that rhabdomyonecrosis occur in animals after experimental poisoning by OP compounds.5,6 This fact has been proven in humans also by several studies.7 So number of recent studies have been carried out using muscle injury parameters like Serum CPK, Serum LDH etc. Some studies have proved the role of serum CPK as a marker of severity and prognosis in adults.

Hence a study of Serum CPK in OP poisoning and comparing this with serum cholinesterase was undertaken.

METHODS

This study was an observational prospective study conducted in a tertiary care hospital over a period of 1 ½ yrs (Nov.2017 to May 2018) after obtaining college ethical committee clearance.

Inclusion criteria

• OP poisoning suspected cases between 1 month to 18 yrs of age within 24 hrs of consumption.

Exclusion criteria

• Patients with carbamate poisoning.
• Other co-existing illness (myopathy chronic renal disease, epilepsy, myocarditis, autoimmune diseases or malignancy or pregnancy).
• Patients who had trauma or received intramuscular (I/M) injection and cardiopulmonary resuscitation recently.
• Patients who are on prior medications like aspirin, anticoagulants, frusemide and dexamethasone.

All the Children (1month to 18 yrs) presented to paediatric department with OP poisoning were enrolled in the study. Out of 36 enrolled cases 2 patients were excluded(one patient presented after 24 hrs and one patient was pregnant). So total 34 cases were included in the study.

After stabilizing the patients and after obtaining written assent, blood was drawn and sent to college laboratory in ice pack for cholinesterase and serum CPK analysis and specific treatment was started. OP poisoning was confirmed by seeing label of the compound and by testing the gastric content in forensic science laboratory. Serum cholinesterase is estimated by kinetic method (DGKC) based on hydrolysis of butrylthiocholine by cholinesterase and serum CPK by kinetic method (IFCC). Blood tests were repeated after 1 week of admission.

Demographic details were collected. Severity of poisoning was graded depending upon the level of the cholinesterase at admission (proud foot classification).8

• Latent cases-cholinesterase level >50% of normal.
• Mild poisoning - cholinesterase level reduces to 20-50% of normal range.
• Moderate poisoning - cholinesterase level reduces to 10-20%.
• Severe poisoning - cholinesterase level reduces to less than10%.

The normal laboratory reference value for serum cholinesterase was 4600-11500 IU/L for males and 3900-10800 IU/L for females. The CDC NHANES (2011-2012) standard values for S.CPK for age and sex was considered as normal reference.

Corresponding median serum CPK values for each severity group were found out. Correlation between cholinesterase and serum CPK was done according to spearman’s rho correlation. Serum CPK values and S.Cholinesterase values were measured after 1 week in all patients. Patients were divided into survivors and non survivors. Values were compared between these two groups.

Statistical analysis

The results were averaged (mean + standard deviation) for continuous data and number and percentage for dichotomous data are presented in Tables. Normality assumption of the data was tested using Shaipro-Wilks test. In this study data was not normally distributed so nonparametric test was used to compare between the groups (Table 1).

Comparisons of Mean/Median values between the study groups were compared using Krushkal Vallis Test and pairwise comparison between the study groups using Mann-Whitney test. Correlation between Serum cholinesterase and S. CPK values were assessed using Spearmans coefficient p value <0.05 considered as statistically significant.
RESULTS

Demographic and general characteristics of study population: A total of 34 children with OP poisoning were included in the study and this comprised 0.5% of the total paediatric admission during the study period. Out of 34 OP poisoning cases, 13(38.2%) were males and 21(61.8%) were females. Mean age of the study population was 12.6±4.25 yrs. Mean time of arrival was 5.76±3.3hrs. Most commonly used compound was chlorpyrifos 13(38%) cases (Table 2).

Table 1: CDC NHANES (2011-2012) normal reference values of serum CPK (for age and sex).

| Age     | Male(IU/L) | Female(IU/L) |
|---------|------------|--------------|
| 0-5yrs  | 41-277     | 34-204       |
| 5-10yrs | 54-269     | 44-189       |
| 10-15yrs| 38-255     | 28-170       |
| >15yrs  | 22-334     | 22-199       |

Table 2: Demographic characteristics.

| Characteristics | n(%)     |
|-----------------|---------|
| Gender          |         |
| Female          | 21(61.8%) |
| Male            | 13(38.2%) |
| Compound        |         |
| Chlorpyrifos    | 13      |
| Dimethoate      | 5       |
| Quinalphos      | 3       |
| Propafenos      | 3       |
| Monochrotophos  | 2       |
| Methylparathion | 2       |
| Chlorovas       | 1       |
| FSL proven      | 4       |
| Phorate         | 1       |

Table 3: Median serum CPK in each severity group at admission.

| Severity (acc. to Cholinesterase level ) | N  | Median S.CPK(IU/L) | Min | Max | p-value* |
|----------------------------------------|----|-------------------|-----|-----|---------|
| Mild                                   | 6  | 276.5             | 81  | 988 | 0.015   |
| Moderate                               | 8  | 308.0             | 138 | 906 |         |
| Severe                                 | 14 | 467.0             | 162 | 5450|         |
| Latent                                 | 6  | 121.5             | 65  | 200 |         |

Figure 1: Correlation of serum cholinesterase and serum CPK at admission.

According to Proudfoot classification we had 14(41.17%) severe cases, 8(23.5%) moderately severe cases, 6(17.6%) mild cases, and 6(17.6%) latent cases. The respective median serum CPK values were 467 IU/L, 308 IU/L, 276.5 IU/L, 121.5 IU/L. There was a statistically significant rise in serum CPK as the severity increased with p value 0.015 (Table 3). The correlation between S.CPK and S.cholinesterase was found out. A strong negative correlation between serum CPK and S.Cholinesterase at admission was observed.

Spearman’s rho coefficient of correlation was -0.522 (p value0.002), which was also significant (Figure1). Out of 34 patients, 6 patients died. Mortality rate was 17%. 3 died before 1 week and the other 3 patients died after 1 week. S.CPK values were compared between survivors and non survivors after 1 week (Table.4). In non survivors it was very high, 2498 IU/L when compared to survivors (201 IU/L) with p value 0.014. Similarly S.Cholinesterase was 1984 IU/L in survivors and 190 IU/L in non survivors. The difference was significant with a p value 0.003 (Table 5). The low S.Cholinesterase and high S.CPK in non survivors are indicative of poor prognosis. We followed up the S.Cholinesterase and S.CPK levels in both the groups. In survivors S.Cholinesterase value improved from 574 IU/L to 1984 IU/L by 1 week. In non survivors, the values further decreased from the admission value, that is from 368.5IU/L to 190 IU/L(Table 6).In case of S.CPK values , no rise was observed in survivors, whereas in non survivors the values increased from 385 IU/L to 2498 IU/L (Table 7). This again indicates that a falling trend in S. Cholinesterase and a rising trend in S.CPK is associated with mortality.
DISCUSSION

From the demographic details it is evident that most of the cases was in adolescent age group and majority were females. This is in agreement with the study by Sen R et al which also showed female preponderance (57 Vs 43).

But in Study by K. Bhattacharya males outnumbered females by a ratio of 2:1. Both these studies where done in >15yrs. The most common compound was chlorpyrifos in our study, which varies depending on the local availability.

Table 4: Comparison in serum CPK in survivors and non survivors at 1 week.

| Serum CPK | Outcome | N  | Median(IU/L) | Min. | Max. | p-value |
|-----------|---------|----|--------------|------|------|---------|
| Week 1    | Survivors | 28 | 201.00       | 16   | 6412 | 0.014   |
|           | Non survivors | 3  | 2498.00      | 761  | 28000|         |

Table 5: Comparison of serum cholinesterase in survivors and non survivors at 1 week.

| S. Cholinesterase | Outcome | N  | Median(IU/L) | Min. | Max. | p-value |
|-------------------|---------|----|--------------|------|------|---------|
| Week 1            | Survivors | 28 | 1984.50      | 178  | 9500 | 0.003   |
|                   | Non survivors | 3  | 190.00       | 150  | 332  |         |

Table 6: Follow up S. Cholinesterase levels in survivors and non survivors.

| Outcome          | S. Cholinesterase | N  | Median(IU/L) | Min. | Max. | p-value |
|------------------|-------------------|----|--------------|------|------|---------|
| Survivors        | Admission          | 28 | 574.00       | 137  | 7739 | 0.004   |
|                  | Week 1             | 28 | 1984.50      | 178  | 9500 |         |
| Non survivors    | Admission          | 6  | 368.50       | 153  | 1013 | 0.262   |
|                  | Week 1             | 3  | 190.00       | 150  | 332  |         |

Table 7: Follow up S.CPK levels in survivors and non survivors.

| Outcome          | Serum CPK          | N  | Median(IU/L) | Min. | Max. | p value |
|------------------|--------------------|----|--------------|------|------|---------|
| Survivors        | Admission          | 28 | 200.00       | 65   | 2008 | 0.812   |
|                  | Week 1             | 28 | 201.00       | 16   | 6412 |         |
| Non survivors    | Admission          | 6  | 385.00       | 162  | 5450 | 0.167   |
|                  | Week 1             | 3  | 2498.00      | 761  | 28000|         |

In the present study, serum CPK value increased as the severity increased. That is the moderate and severe groups had high S.CPK values suggesting muscle injury. This is in agreement with the study done by Nermee et al, in 2-53 yrs age group which also showed a significant rise in serum CPK in more severe cases.7

M John et al, had shown that muscle injury was seen in all OP poisoning patients beginning at admission, peaking over first 5 days and declining over the next 5 days and blood muscle isoenzymes were relatively high in more severe cases.5

The present study showed a strong negative correlation between serum cholinesterase and serum CPK at admission. In a similar study conducted by Nermee et al, in 2-53 yrs age group, butyryl cholinesterase and serum CPK had a highly significant negative correlation with coefficient of correlation, r of -0.810. K.9

Battacharya et al, had studied the correlation between serum CPK and erythrocyte cholinesterase which showed a very strong negative correlation with r -0.832 in >16 yrs age group.10

We had divided the patients to survivors and non survivors. The present study showed that after 1 week of admission, there was a significant difference in cholinesterase as well as serum CPK between these groups. In survivor’s cholinesterase levels improved from admission value whereas in non survivors it decreased further. Similarly, serum CPK level increased in non survivors and there was no such rise in survivors, presumably due to the persisting muscle injury and myonecrosis in lethal cases.

In the study conducted by Sen R et al, serum cholinesterase was progressively increasing both in survivors and non survivors.11 S.CPK was decreasing in both the groups, but not significantly in non survivors and it was persistently higher in non survivors (>900 IU/L).
The present study shows serum CPK is a very good lab parameter in OP poisoning both as severity marker and as a prognostication marker.

CONCLUSION

S.CPK has a strong negative correlation with Serum Cholinesterase in OP poisoning at admission. So, S.CPK can also be used as a severity marker in OP poisoning. And the rising trend of S.CPK and a falling trend of S. Cholinesterase indicates severe poisoning, so it can be used for prognostication and to anticipate complications.

Sample size was very less. That is the limitation of this study.

Recommendations

Serum CPK levels need to be evaluated and followed up in OP poisoning cases in children to know the severity and for prognostication. The incidence of OP poisoning cases in Paediatric age group are less, hence needs more similar studies on S.CPK in OP poisoning.

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