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A prospective study on CPK levels in tetanus

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Abstract*: Tetanus, an infectious disease, characterized by progressive spastic paralysis of multiple groups of muscles, is caused by a gram positive, obligate, anaerobic organism, Clostridium tetani. The organism produces a neurotoxin, tetanospasmin, which interferes with neurotransmitter release to block inhibitor impulses thereby leading to unopposed muscle contraction, spasms and peripheral muscle rigidity. The spores of Clostridium tetani which are ubiquitously distributed in environment can contaminate the wound and lead to tetanus. Since culture of Cl.tetani is labor intensive, the diagnosis is entirely clinical. An iso enzyme, Creatinine phospho kinase (CPK) is known to be elevated in tetanus. In the present study, an attempt has been made to correlate CPK levels with morbidity and mortality in tetanus patients. The study comprises of analysis of clinical data of nineteen patients admitted at SRRIT&CD, Hyderabad, an infectious diseases hospital, over a period of one year from Nov 2014 to Oct 2015, in relation to serum CPK levels at weekly intervals from admission to discharge/death of the patient. Ten patients recovered and discharged while nine died within 1-2 days post admission. All patients showed significantly raised levels of CPK at the time of admission and the levels tapered over four weeks in those who survived the infection. The patients who died within 1-2 days of admission had significantly high levels of CPK. The study concludes that periodic estimation of CPK can serve as a valuable prognostic tool in management and as a predictor of mortality in tetanus.*

Keywords: *Clostridium tetani, Creatinine phospho kinase, Neurotoxin, Tetanus, Trismus.*

I. Introduction

Tetanus is a highly lethal infectious disease caused by a neurotoxin, tetanospasmin, produced by gram positive anaerobic bacillus Clostridium tetani. Its clinical picture is caused by over activity of somatic motor neurons induced by the exotoxin[1]. Although tetanus has become rare in developed countries due to successful implementation of immunization, the disease is still prevalent in developing and under developed countries[2].

Muscle rigidity and spasms constitute the typical clinical hallmarks of generalized tetanus[1]. Unrecognized tetanus may rapidly progress into a critical condition with severe muscle spasms, autonomic dysfunction and/or respiratory failure[3]. Patients with a clinical suspicion of tetanus must therefore, in addition to receiving local wound care, antibiotics and tetanus immunoglobulins need to have their serum tested for CPK levels as the levels may be increased[4] early in course of disease even before onset of spasms[5] due to toxin induced changes in the permeability of the muscle fiber membrane leading to muscle hyperactivity[2, 5]. Since CPK levels may help to detect inappropriate muscle relaxation, high initial CPK levels followed by a decline not only indicate but can serve as a prognostic indicator of muscle activity allowing for adjustments of drug dosage[6] in disease management.

II. Aims and objectives

1. To study the clinical prognosis and cpk levels in tetanus
2. To assess the severity of the disease in relation to cpk levels
3. To monitor the response to treatment in relation to cpk levels
4. To study the mortality and disease outcome in relation to cpk levels

III. Materials and methods

The study was started after procuring Institutional ethics committee clearance. All cases (19) with clinical diagnosis of tetanus based on history of recent injury/ bites/ abortion/ delivery/ burns/ symptoms and signs which include inability to open mouth, generalized or local spasms, trismus, Risus sardonicus, neck rigidity and opisthotonus admitted at SRRIT&CD from November 2014 to October 2015 were **included** in the study.

Any patient with pre existing co morbid conditions that may lead to raised CPK, like myocardial infarction, pulmonary embolism, myositis, muscular dystrophies, epilepsy, meningitis, peritonitis myxoedema were excluded from the study.

All patients were kept in a noise free isolation ward and specific treatment consisting of local wound care, tetanus immuno globulins, tetanus toxoid, muscle relaxants, antibiotics and IV fluids calculated based on body weight was started. Peripheral venous blood for CPK estimation, CBP, blood urea, serum creatinine, serum electrolytes and urine for complete examination were collected.

CPK level was estimated by N-acetyl cysteine (NAC) activated method, Kinetic (method of Olive, modified by Rosalki and Szasz)

Tests were done on fully automated analyzer Erba XL 640.

Values interpreted as per the standard reference ranges[7].

Principle of the test[7]:

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow{\text{CK}} \text{Creatine} + \text{ATP}$$

$$\text{ATP} + \text{Glucose} \xrightarrow{\text{HK}} \text{Glucose-6-phosphate} + \text{ADP}$$

$$\text{Glucose-6-phosphate} + \text{NAD} \xrightarrow{\text{G6PDH}} \text{Gluconate-6-P} + \text{NADH+H+}$$

Expected values[7]:

Male: 46 – 171 U/l Female: 24 – 145 U/l Children: Umbilical cord blood 175 - 402 U/l Newborns 468 - 1200 U/l ≤ 5 days 195 - 700 U/l < 6 months 41 - 330 U/l > 6 months 24 - 229 U/l

The tests were repeated at weekly intervals for the surviving patients who recovered with treatment and were discharged at the end of four weeks.

IV. Results

Out of nineteen patients admitted with tetanus, two were below five years age, one boy and one girl. Eleven patients were aged below fifteen - seven boys and four girls; two males and two females were fifteen to forty years old while there were one female patient aged fifty five years and a sixty year old male patient (Table).

All patients presented with H/O injury, inability to open mouth, spasms, both generalized and local, trismus, Risus sardonicus, neck rigidity and mild to severe opisthotonus at the time of admission.

All patients received local wound care, tetanus immunoglobulins, tetanus toxoid, antibiotics, IV diazepam infusion for muscle relaxation and sedation, $MgSo_4$[8] to control autonomic dysfunction wherever indicated, IV fluids, nutritional and general supportive care.

Table: showing age, gender, clinical features and CPK levels of 19 patients.

Age in years	No. of cases	M	CPK level	F	CPK level at admission	Deaths	CPK level 1st week	CPK level 2nd week	CPK level 3rd week	CPK level 4th week
<5	2	1	299 IU/ml	1	356 IU/ml	-	185, 212	72, 142	56, 64	34, 45
5-15	11	7	276-1340	4	371-1258	5	182-286	106-286	42-84	35-58
16-40	4	2	954,2315	2	1950,2216	3	482	186	102	56
>40	2	1	1284	1	3698	1	785	155	40	34
Total	19	11		8		9				

Out of 9 patients who died within 1-2 days of admission, one girl and one boy were 5 yrs old, one boy was 14 yr old, one boy and one girl were <10 yrs, one male and two females were <20 yrs and one woman was 55 yrs old. All of them showed high levels of serum CPK ranging from 958-3698 IU/ml at the time of admission.

Death was mostly due to severe tetanus associated with severe muscular spasm and opisthotonus leading to respiratory failure.

Ten patients recovered and were discharged at the end of four weeks.

Other investigations which included blood urea, serum creatinine, serum electrolytes, CBP, RBS and CUE were normal in ten patients who recovered, while the tests could not be performed for nine patients who died soon after admission.

V. Discussion

Creatinine phospho kinase is an intracellular iso enzyme present in greatest amounts in skeletal muscle, myocardium, and brain; smaller amounts occur in other visceral tissues[9]. Serum Creatinine phospho kinase

levels are estimated to assess damage to skeletal muscle, heart or brain[5]. Normal level of CPK is 60-174 and any value above 174 IU/L was considered abnormal[10].Standardized methods for the determination for CK using the "reverse reaction" and activation by NAC were recommended by the German Society for Clinical chemistry (DGKC) and the International Federation of Clinical Chemistry (IFCC), in 1977 and 1990 respectively. This assay meets the recommendations of the IFCC and DGKC[7].Increased CPK levels may be found in tetanus, the enzyme possibly originating from the convulsing muscle tissue probably as a result of changes in muscle fibre membrane permeability caused by tetanus toxin[1].

The importance of increased serum CPK levels in tetanus was first reported in 1960[11]. Once tetanus toxin enters the blood, CPK release occurs 3 to 4 days before muscle stiffness develops[12]. A high CPK, or one that goes up from the first to the second or later samples, generally indicates that there has been some recent muscle damage[13]. Serial test results that peak and then begin to drop indicate that new muscle damage has diminished, while increasing and persistent elevations suggest continued damage[14].

The present study showed similar observations where in there was a progressive decrease in CPK levels in ten patients over four weeks time at the end of which they showed signs of complete recovery. This indicates decreased muscle damage which can be taken as a direct evidence of improvement with treatment and better prognosis.

CPK levels were found to be significantly elevated in the range of (1258-3698 IU/L) in nine patients who died within 1-2 days of admission.

Conclusions:

Serum CPK, a simple test which is cost effective and not labor intensive, can serve as an effective laboratory tool in tetanus to

1. Assess the prognosis of the disease.
2. To monitor the response to treatment which may require daily estimation of CPK levels to detect insufficient muscle relaxation, allowing for dosage adjustment.
3. Predict disease outcome.

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