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CREATININE PHOSPHOKINASE; A PREDICTIVE BIOCHEMICAL MARKER FOR COMPARTMENT SYNDROME

Medical Biochemistry

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KEYWORDS

CPK, Compartment Syndrome(CS), Compartment Pressure(CS)

INTRODUCTION

Acute compartment syndrome is a condition in which there is increased pressure within a closed osteofascial compartment, resulting in impaired local circulation. Acute compartment syndrome is considered a surgical emergency. Without prompt treatment, acute compartment syndrome can lead to ischemia and eventually, necrosis.

Generally, acute compartment syndrome is considered a clinical diagnosis. However, intracompartmental pressure (ICP) > 30 mmHg can be used as a threshold to aid in diagnosis. However, a single normal ICP reading does not exclude acute compartment syndrome. Fascia is a thin, inelastic sheet of connective tissue that surrounds muscle compartments and limits the capacity for rapid expansion. In the leg, there are four muscle compartments: anterior, lateral, deep posterior, and superficial posterior. The anterior compartment of the leg is the most common location for compartment syndrome. This compartment contains the extensor muscles of the toes, the tibialis anterior muscle, the deep peroneal nerve, and the tibial artery

Acute compartment syndrome can occur with any condition that restricts the intracompartmental space or increases the fluid volume in the intracompartmental space. Acute compartment syndrome can occur without any precipitating trauma but typically occurs after a long bone fracture, with tibial fractures being the most common cause of the condition, followed by distal radius fractures. Seventy-five percent of cases of acute compartment syndrome are associated with fractures. After fractures, the most common cause of acute compartment syndrome is soft tissue injuries. Other causes of acute compartment syndrome include burns, vascular injuries, crush injuries, drug overdoses, reperfusion injuries, thrombosis, bleeding disorders, infections, improperly placed casts or splints, tight circumferential bandages, penetrating trauma, intense athletic activity, and poor positioning during surgery. In children, supracondylar fractures of the humerus and both ulnar and radial forearm fractures are associated with compartment syndrome.

The incidence of acute compartment syndrome is estimated to be 7.3 per 100,000 in males and 0.7 per 100,000 in females, with the majority of cases occurring after trauma.

Pathophysiology

Acute compartment syndrome occurs due to decreased intracompartmental space or increased intracompartmental fluid volume because the surrounding fascia is inherently non-compliant. As the compartment pressure increases, hemodynamics are impaired. There is normally an equilibrium between venous outflow and arterial inflow. When there is an increase in compartmental pressure, there is a reduction in venous outflow. This causes venous pressure and, thus, venous capillary pressure to increase. If the intracompartmental pressure becomes higher than arterial pressure, a decrease in arterial inflow will also occur. The reduction of venous outflow and arterial inflow result in decreased oxygenation of tissues causing ischemia. If the deficit of oxygenation becomes high enough, irreversible necrosis may occur.

The normal pressure within a compartment is less than 10 mmHg. If the intracompartmental pressure reaches 30 mmHg or greater, acute compartment syndrome is present. However, a single normal ICP reading does not exclude acute compartment syndrome. ICP should be monitored serially or continuously.

Given the prevalence of CS following extremity fracture, the difficulty in timely diagnosis and the ramifications of a delay in diagnosis, a precise, reliable, and non-invasive means for early diagnosis is needed. Time of decompressive fasciotomy is a crucial factor in any case of adult CS and is especially important in paediatric CS. Basic research has shown that ischemia begins as soon as 4 hours after elevated intracompartmental pressure (ICP) and that 8 hours of elevated pressures can induce irreversible tissue necrosis**.**

Creatine kinase (CK) also known as creatine phosphokinase (CPK) or phospho-creatine kinase, is an enzyme expressed by various tissues and cell types. Although elevated serum CK titer is known to be associated with muscle injury, it is unknown if there is a threshold level highly associated with CS. This study was aimed to analyse the SCK level in patients with clinical CS.

MATERIAL AND METHODS

All the patients who were admitted in the emergency department with diagnosis of compartment syndrome were included in the study and serial serum CPK levels were measured immediately before fasciotomy and then 24 hours of the surgery then at 1 and 2 weeks of the surgery.

A total of 50 patients were included 28 males and 22 females.

Inclusion criteria

Patients with clinically suspected to have acute Compartment Syndrome of both sexes

Exclusion criteria

Patients with congenital heart disease,
Rhabdomyolysis
Muscular dystrophy
Autoimmune disease
Pathological fracture,
Acute kidney injury and known neurological cases
Immuno-compromised patients
Non-willing patients

Statistical Analysis:

RESULTS:

In this study of 2 weeks duration, a total of 49 patients were enrolled in the final analysis. The study sample consisted of 27 males and 22 females and the mean age of study participants was recorded as 19.94 $\pm$ 9.4 years

To get a general insight about the distribution and the trend of the CPK levels at different time points descriptive analysis was performed and various statistics were calculated (Table 1). For quick visual comparison of the distribution of variables the Strip Plot was also sketched Fig.2

Comparison was performed using Friedman's test showing a statistically significant decrease in the CPK levels before and after the surgery, $\chi 2(3) = 147$, $p<0.001$. (Table 1, Fig 4).

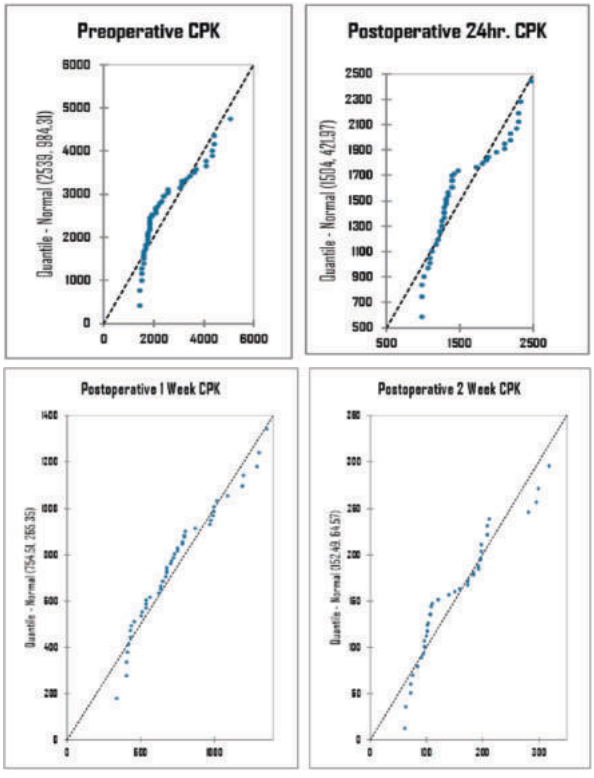

Fig 1: QQ plot shows data not normally distributed

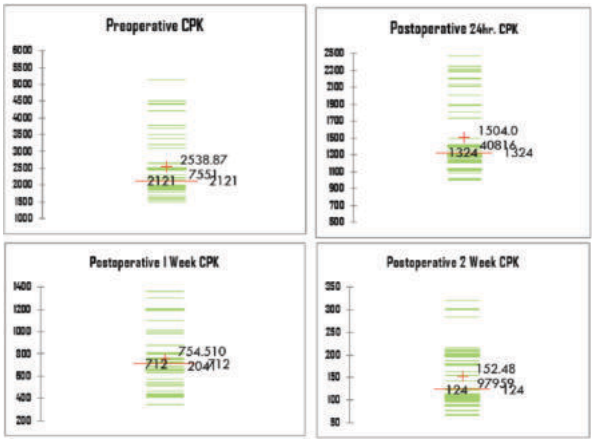

Fig 2: Plot showing data points not evenly distributed around centre line

However from Fig 3, it can be clearly seen that CPK levels have dramatically decreased for each of the patients under study with the advancement in time since surgery.

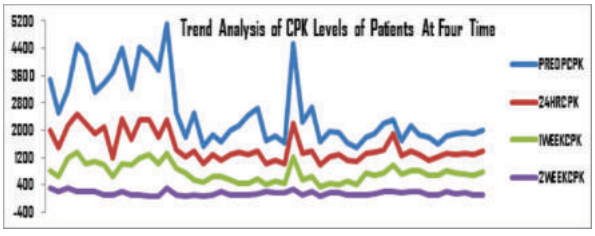

Fig 3: Trend analysis of CPK levels pre operatively and post operatively.

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Table 1: Descriptive Statistics and Friedman ANOVA to test the hypothesis of same distribution for the four time points.

Variables	Mean	Standard Devaition	Q1	Median	Q3	Minimum	Maximum	Mean Rank	p-value
	2538.88	994.507	1831	2121	3200	1498	5122	4	<0.001
24hr. Postoperative CPK	1504.04	426.348	1234	1324	1810	998	2467	3	
1 Week Postoperative CPK	754.51	268.097	543	712	981	342	1365	2	
2 Week Postoperative CPK	152.49	65.237	102	124	198	65	321	1	

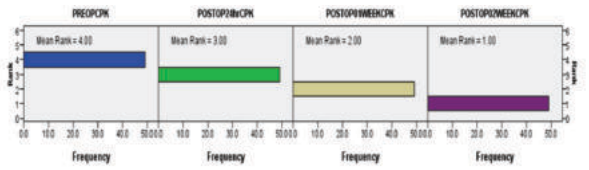

Fig 4: Friedman's ANOVA by Ranks

Post-hoc analysis with Wilcoxon Signed-Rank test was conducted with Bonferroni correction applied, resulting in a significance level set at p<0.001 (Table 2

Table 2: Pair-wise comparison

Sample 1 v/s Sample 2	Test Statistics	p-value
Postoperative 02 Week CPK v/s Postoperative 01 Week CPK	3.834	<0.001
Postoperative 02Week CPK v/s Postoperative 24hr. CPK	7.668	<0.001
Postoperative 02Week CPK v/s Preoperative CPK	11.502	<0.001
Postoperative 01 Week CPK v/s Postoperative 24hr. CPK	3.834	<0.001
Postoperative 01 Week CPK v/s Preoperative CPK	7.668	<0.001
Postoperative 24hr. CPK v/s Preoperative CPK	3.834	<0.001
*Each row test the null hypothesis that the sample 1 and sample 2 distributions are the same.		
*Significance level is 0.05		

DISCUSSIONS

The Compartment Syndrome of the limb is difficult to diagnose especially in the pediatric age group and presents as a surgical emergency. Significant muscle damage can occur with CP >30 to 40 mmHg or within 10 to 30 mmHg of diastolic BP and is considered as a strong indicator for fasciotomy. Accurate measurement of CP(compartment pressure) is user dependent and there is no consensus on values to define CS. So, due to difficulty in diagnosis within time and ramifications of a delay in diagnosis, a precise and reliable means for early diagnosis is needed.

In the present study, we hypothesized that as the severe muscle breakdown causes a significant SCK elevation, so significant elevated level of SCK may be found in Acute CS which might be directly proportional to the CP(compartment pressure). In the present study, we observed a significantly raised level of CPK in cases of compartment syndrome. Our observation shows approximately 18-20 fold raises in serum CPK levels. Therefore, our finding concluded that the serum CPK level may be used as a potential predictive biomarker to diagnose the CS(compartment syndrome) as an adjuvant to clinical diagnosis to decide the intervention.

In reference to our study observations, the finding of elevated CPK with Compartment Syndrome is plausible. The SCK is stored in muscle cells and the cellular ischemia ensues when compartment pressure exceeds capillary pressure. Although ischemia would be expected to generate cellular debris, including the liberation of CPK from cells. As the extremities have the large muscle mass, it is likely

possible to mark the sudden rise in CPK as one of the early diagnostic/prognostic biomarker for CS.

As per our study observations, some other studies such as Lampert, et al. (1995), who reported two cases of compartment syndrome of the lower leg. During sedation and mechanical ventilation CPK activity of more than 8,000 U/l was found in both patients. After extubation, clinical symptoms of the compartment syndrome were found. In another retrospective study, Ihedioha et al. (2005) in patients with compartment syndrome. Their observations suggested that although raised CPK levels are not diagnostic, they are a useful adjunct in making a diagnosis. Therefore, CPK estimation should be done in patients with suspected compartment syndrome. Moreover, an early fasciotomy (<12 hours) has significantly lowered the elevated CPK levels, confirming the view that the earlier the decompression, the lesser the muscle damage. Liu, et al. (2009) in a study observed 20 times more elevated CPK level at two hours after injury than in normal patients. Twenty-four hours later, CPK reached its maximum of about 42 times more than the normal. After one week, the value CPK recovered to a normal level. However, the pathological changes of muscle were irreversible. They concluded that an alteration in CPK level can reflect the progression of disease objectively. If it increased sharply, the chance of compartment syndrome was high. Therefore continuous monitoring the dynamicity of CPK after injury can provide an assistant for early diagnosis of compartment syndrome and evaluating the pathogenesis of the condition. In the latest study by Valdez, et al. (2013), out of 97 patients with isolated tibia/fibula fracture, 39 had CS . They observed in a univariate and also in the multivariate model, CPK level greater than 4,000 U/L is highly associated with CS.

CONCLUSION

We concluded that SCK level may use as a potential predictive biomarker to diagnose the CS as an adjuvant to clinical diagnosis to decide the intervention.

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