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Investigating Correlation of Lower Extremity Muscle Compartment Syndrome with Muscle Related Serum Enzyme Tests: Is any Reliable Biomarker?

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ABSTRACT

Specific muscle related biomarker might better diagnose the compartment syndrome towards lessen complications. The trial assessed the issue of it's determining. 149 referral cases of lower extremity injuries were recruited for two sectional assessment of their muscle compartment pressures and simultaneously measurement of serum CPK, LDH, AST (SGOT), Troponin and urine Myoglubin levels. Successive compartment pressure with ΔP recording with timed blood samples were considered on first visit, pre and postoperative and pre-discharge periods. Data were analyzed in fasciotomized patients had acute compartment syndrome for any meaningful biomarker.122 patients (81%) had lower extremity trauma and 27 cases (19%) had thrombo-embolic vascular events. Outcomes revealed 14 cases that required fasciotomy with the pressure ranges of 35-53 mmHg (mean=46, SD=5.8) and ΔP 24.71 (min=18, max=31, SD= 4.02) before fasciotomy and finally 4 amputations. All above muscle related enzyme tests had maximum thresholds before fasciotomies. Troponin was positive in 3 (21.4%) cases and Urine Myoglubin was positive in 13 patients (92.9%) of 14 fasciotomy. There was no correlation between serum enzyme tests and acute compartment pressures and also with outcome and the type of injuries before fasciotomy as a definite biomarker. Fasciotomy requirement was correlated significantly with tests in all other defined periods ($P \leq 0.007$).We could not statistically find any biomarker to be specified. Significant optimum of serum CPK, LDH and AST before fasciotomy alongside highly positive Myoglubin in them conclude that their measurements are crucial in promoting diagnosis and consequently we claim that sum of thresholds could be more reliable than existence of a biomarker alone.

Keywords: Compartment syndrome biomarker, CPK, LDH, Troponin, Urine Myoglubin.

INTRODUCTION

Lower extremity trauma with producing acute Muscle Compartment Syndrome (MCS) is a known devastating complication require fast diagnosis and repair for precluding its debilitating outcome. The least result of progressive and insidious increased intra compartment pressure is relative loss of normal limb activity or even amputation in any indicated levels. Although, MCS has been widely researched, yet there is not any determined biomarker to deserve reliable consideration for diagnosis[1]. Therefore, the prospect of being a time specified sub group co-efficient blood enzyme parallel to peak compartment pressure or perhaps a specific supra selective

dependent muscle cell end metabolic marker for blood confirming MCS is still frustrated. So, the conception pessimistically emerges that the issue may be 'far from our experience' or promisingly on the other sight, blood enzyme markers may not be enough to correlate at the time of a fixed compartment syndrome or perhaps their releasing in blood stream may be postponed by pathophysiologic blockage of extremity venous back flow by compartment pressure. Given the fluctuating clinical status and thresholds in MCS, although expecting a specified muscle cell enzyme might not be anticipated in pre-critical levels, but in acute peaked situation may not be far from the expectation. The current knowledge of blood detectable cell enzymes is now well recognized during inflammatory processes and so in progressive resultant ischemia. Therefore, research for any concept toward the issue is principally accessible. For succeeding, seems that traumatic limbs and damages need to be considered on time, because it seems that a wide range of physiologic muscle responses is insidiously overcome by muscle cell tolerance that prevent prompt diagnosis of Acute Compartment Syndrome (ACS). In this serious situation cell damage and necrosis during a short time will happen[1-2] and thus muscle related serum enzymes raise according to the impairments. At present, effective existed methods for Intra Compartment Pressure (ICP) measurements accompanied by close physical examinations warrant a reliable clue to emphasize on timely pressure releasing procedure such as fasciotomy in ACS. But, the problem is that the procedure may not usually end to complete recovery of the extremity. Based on the outcome, in spite of these methods, there is still a real sensible deficiency of certain diagnosis of ACS in traumatic limbs. Hence, determining of more accurate verifiable indicator is imperative. For this purpose, the aim of the study was designed to investigate the available especial muscle related laboratory tests concomitant with successive and interval ICP measurements in traumatic patients with lower extremity injuries and vascular thrombo-embolic accidents who were referred and were progressed ACS during management in order to determine a reliable biomarker.

METHOD

This was the second part of a two sectional prospective clinical trial, which was performed in 149 (119 Males, 30 females) cases of lower extremity trauma who were referred to our emergency, orthopedic, trauma and vascular departments of hospitals affiliated to Jundishapour University of Medical Science, Ahwaz, Iran, during one year from May 2014. Patients were recruited on the basis of the aim of the whole study for defined periodic measurements of ICP during admission and lower extremity trauma management until discharge; to find critical ICP ranges that were required fasciotomy performance and also investigating selected muscle related laboratory enzyme tests to determine any correlated biomarker in the time of fasciotomy indication as the second part of the trial. All the patients gave their informed consents before enrolment in the study based on ethical approval conform to the guidelines of 1975 declaration of Helsinki and approved research project of institution, No: U- 92050, faculty registration No: D/826. Inclusion criteria were patients with severe lower extremity trauma and femoral-tibial thrombo-embolic events. Exclusion criteria were crush and wide-open muscular injuries and who were required amputations. Troponin, Creatine Phospho-Kinase (CPK IU/L), Lactate Dehydrogenase (LDH IU/L), Aspartate Aminotransferase (AST U/L)(SGOT) and Urine Myoglubin (UM) were selected and included for measurement and evaluation as available and reliable selective muscle cell related controlling enzyme tests upon their laboratory methods. Laboratory test samples parallel to ICP measurements were taken in admission, before and after required operation for treatment, before fasciotomy and before discharge. ÄP (diastolic pressure minus intra compartment pressure) was considered too and was calculated alongside the ICP. For Troponin and UM, because of more rarity in confronting to other selected tests, we primarily used qualifying kits for determining positive cases then in positive patients the quantities were provided in the percentage of positiveness as comparing values. Collected data were analyzed for differences and their significance and

correlations during aforementioned defined periods in patients were involved in ACS and were required calf fasciotomy releasing technique, through Chi square (Pearson) and ANOVA (post hoc) tests by SPSS, version 20 software.

RESULTS

from patients in the study, 122 cases (81%) were lower extremity trauma and 27 cases (19%) had vascular injuries and thrombo-embolic accidents. Outcome of patients after treatment revealed 117 full-recovered patients to normal status, 14 complicated mild to severe foot activity and 14 cases of fasciotomized limb because of ACS with the pressure ranges of 35-53 mmHg (mean=46, SD=5.8) and ÄP 24.71 (min=18, max=31, SD= 4.02) before fasciotomy and finally 4 BK amputations. Also, from 14 fasciotomies 4 lower mid foot and toes amputations were required. Troponin in admission and before discharge periods was in normal range, but before fasciotomy in 3 (21.4%) cases of 14 patients and also in 5 patients of 147 post operative controls was positive and above normal range. Urine Myoglubin (UM) was positive in 5 cases (3.35%) of 149 patients in admission, 32 cases (22.06%) of 145 patients in postoperative period, 13 patients (92.9%) of 14 fasciotomized

Table 1: Investigated laboratory enzyme tests results. Ranges and mean measurements in defined periods of the study

Defined periods	CPK.Creatine Phospho Kinase.	LDH.Lactate Dehydrogenase	AST (SGOT)Aspartate aminotransferase	Troponin	UMUrine Myoglubin
First visit (admission)	215.55(min=21, max=1000, SD=219.36)	200 (min=23, max=980, SD= 223)	53 (min=11, max=387, SD=57)	No Positive	5+ From 149 cases
Post Operation	1415(m9n=121, max 7600, SD=1303)	1024 (min=98, max=4500, SD=800)	13 (min=32, max=600, SD=96)	5+ From 147 cases	32+ From 145 cases
Before fasciotomy	7908 (min=3900, max=12600, Sd=2876)	5227 (min=2300, max=8700, SD=2107)	276 (min=102, max=459, SD=103)	3+ From 14 cases	13+ From 14 cases
Before discharge	312(min=37, max=2400, SD=325)	339 (min=41, max=1897, SD=267)	51 (min=18, max=213, SD=29)	No Positive	1+From 149 cases

Table 2: Correlations of muscle enzyme tests with compartment pressure and ÄP before fasciotomy

Variables	Laboratory result (Mean)	Statistics	Before fasciotomy			
				ICP	ΔP	
CPK	7908 (min=3900, max=12600, SD=2876)	Pearson correlationSig. (2-tailed)N14	-.122	-.194	.678	.505
LDH	5227 (min=2300, max=8700, SD=2107)	Pearson correlationSig. (2-tailed)N14	.105	-.055	.722	.851
AST (SGOT)	276 (min=102, max=459, SD=103)	Pearson correlationSig. (2-tailed)N14	.325	-.306	.256	.287

cases and in 1 case (0.67%) of 149 patients before discharge. Measurement results of laboratory muscle enzyme tests revealed high maximum quantity of CPK, LDH and AST in fasciotomy periods in comparing to the other defined durations (Table 1), but no correlations with ICP and ÄP before fasciotomy periods were achieved (Table 2).

The Outcome was not correlated with the enzyme tests in fasciotomized patients (Table 3 supplementary file). AST independently was also shown higher quantity in post-operative period of main surgical management of overall patients as maximum threshold and the minimum or normal rang in admissions. Fasciotomy requirement as a significant statistic index was obtained correlated with serum enzyme tests in all other defined periods than before fasciotomy in the study (Table 4 supplementary file). Comparing the type of injuries to laboratory tests for correlation was also negative before fasciotomy (Table 5 supplementary file). From

Table 3:Correlation of extremities outcome with Muscle related enzyme tests before fasciotomy (refer supplementary file)

	Variables	P values
Post Hoc	CPK	.834
Tests	LDH	.545
(ANOVA)	AST (SGOT)	.072
Chi-square	U.Mioglobin	.260
Test		

Table 4: Correlation of blood muscle enzyme tests with fasciotomy requirements and outcome in defined periods of the study (refer supplementary file)

Variables	P values
CPK at first visit	0.001
CPK after operation	0.000
CPK before discharge	0.000
LDH at first visit	0.003
LDH after operation	0.000
LDH before discharge	0.000
AST (SGOT) at first visit	0.000
AST after operation	0.007
∆P before discharge	0.000

Table 5: Correlation of muscle enzyme tests with types of trauma before fasciotomy (refer supplementary file)

Variables	P values
CPK	0.776
LDH	0.894
AST (SGOT)	0.238

13 cases of positive UM in fasciotomized patients, 4 cases (30.76%) had amputations. Mean range of CPK in Embolectomized patients in all defined periods was more than blunt and penetrating trauma patients and statistically was shown significant in only post operative time (P=0.027). Laboratory enzyme values in amputated cases after operations and before discharge were higher than complicated feet and full-recovered patients (P=<0.001).

DISCUSSION

Compartment syndrome is a morbid status that simply is ended to extremity mortality and loss. From unexpected states in sporting or prolonged daily malpositioning during extremity activities, to a specific situation such as direct trauma or vascular injuries are the wide ranges of producing MCS. Unconscious positional and prolong inadvertent maintaining of extremities during surgical procedures also has been implicated in MCS with concomitant more complications[3]. A few diagnostic techniques are advocated for MCS in which ICP measurements and close physical examination[1] in spite of doubtful consensus on ICP ranges are the main approaches. Subsidiary ways as blood laboratory tests have been introduced to contain effective diagnostic properties in literature for MCS. Concomitance of Creatine Kinase (CK) activity with surgical position depended procedures has been reported before the year 2000[2]. Recent years besides CK, Lactic acid and Troponin I levels are also postulated to be associated with the development of MCS4. The reported issue has also detailed that compartment syndrome were most strongly associated with Maximum CK, minimum calcium, minimum blood urea nitrogen (BUN), maximum chloride, maximum lactate and minimum of HCO3, in which CK and Chloride with low BUN

in a model had 100% association [3]. Myoglubin presentation in urine and especially in renal pathologic samples inside convoluting tubes as granular casts has shown to lead fatal outcomes in patients involving acute MCS with confirmed elevation of serologic C-Reactive Protein, BUN and serum Creatinine[5]. For limb ischemic situation following MCS, serum Ischemia-Modified Albumin with 81.8% sensitivity and 81.8% specifity has been shown in 81.8% of lower limb ischemia to be useful in diagnosis of subtle clinical ischemic complications[6]. Intra muscular Glucose concentrations and concomitant partial pressure of oxygen tensions have recorded by available commercial probes in animal model for diagnosis of compartment syndrome[7], but its application for human adjustment is not proven. Apart from skeletal MCS, serum Adenosine and Interleukin 10, D-lactate (LDH) have also presented as valid biomarkers in abdominal compartment syndromes reflecting intra abdominal hypertension and intestinal wall ischemia[8-9]. Nevertheless, regarding MCS studies, requirement of more investigations for probable better data justification is still remained. According to the literature, we have supposed that introduced laboratory tests, which have been selected for the study along with simultaneous ICP measurement and ÄP, might achieve better conclusion. Based on the extracted results in the study and demonstration by tables, data were not statistically correlated and were not significant in comparing analysis of all tests that prospect to give a specific correlated biomarker for improvement in diagnosis of MCS. Nevertheless, if the study was not successful in statistic relations, but was produced that the quantity thresholds of laboratory tests were being optimum before fasciotomies that are highly expressive for diagnosis accompanied by critical ICP and ÄP in mentioned duration (Table 1). Mean results of all CPK, LDH and ALT along with positiveness and achieved percentages of UM are in upper limits in comparison with the other defined periods, at the time of fasciotomy requirements. These findings depend on CPK threshold of about 8000 U/L (7908 U/L) and more than 4000U/L as a warning for fasciotomy requirement is completely similar to Lampert R, and Valdez C studies[3,4]. Besides, LDH threshold also is expressed that the quantity about 5200 U/L or more would be alarming for suspicion of MCS. As the ALT (SGOT) test shows generally highly sensitive to wide ranges of injuries and also Troponin is more specific and dependent in cardiac insults, their resulted thresholds require more specific trials; thus, could not insist on their obtained values. Vise versa, we believe that either qualitative or quantitative measurements of UM which produced to be valuable in fasciotomy requirements because of its numerous positiveness in overall fasciotomized patients, is completely enough to be accounted as meaningful as a warning test; its positive consequence can be a guidance for prompt fasciotomy with optimal ICP range and in accordance with CPK and LDH high levels. Consequently, although we could not find any clear statistically approved biomarker in relation to MCS but thresholds of CPK, LDH and UM were shown to be valuable in expecting and requirement of fasciotomy for patients who suffering from lower extremity trauma and concomitant high ICP towards ACS. Therefore, we conclude that the simultaneous control of serum CPK, LDH and UM referring to their thresholds or positiveness, in parallel to ICP and ÄP recording, would be an effective guide for the surgeon to decide better and more promptly. These concluded tests would not be definite biomarkers, but we would rather to denominate them as threshold biomarkers of laboratory tests were considered in the study.

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