IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 12 Ver. I (Dec. 2017), PP 27-33
www.iosrjournals.org

Serum Alkaline Phosphatase, A Prospective Biomarker For Assessment of Progress of Fracture Healing

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Abstract
Introduction: *Bone-specific alkaline phosphatase is a specific marker of osteoblasts and gives a good measure of bone forming activity.[1]bone metabolic units (BMU)are also activated in fracture healing and can be demonstrated quantitatively by estimation of bone turnover markers (BTMs). Serum alkaline phosphatase is a specific marker of osteoblasts and gives a good measure of bone forming activity.*
Aims *:to evaluate the changes in serum alkaline phosphatase levels during healing of isolated femur shaft fractures treated with close reduction and interlocking nail*
Material And methods: *descriptive, prospective and follow up study was conducted in the department of Orthopaedics, SMS Medical College & Attached Hospitals, Jaipur.64 healthy adults of age 18 to 45years with isolated closed fracture femur were included. The patients with any systemic condition, disease, and/or drug intake affecting bone turnover in any manner were excluded from the study. The fractures were closed reduced and internally fixed using an interlocking nail. Allthe patients were followed up every month for 9 months after injury to look for clinico-radiological signs of fracture union. Biochemical monitoring was done The marker ALP was measured using in vitro qualitative measurement by p-NPP method in biochemistry lab.*
Results: *The outcome of the current study is that the serum alkaline phosphastase is suggested as non-invasive aids for monitoring fracture healing. It may help in the monitoring of fracture healing, complementing the clinico-radiological evaluation.*
The detection of volume of callus formed across the fracture site in combination with clinical signs of union remain the gold standard for assessing fracture healing. But early detection of a slow healing or a non-healing fracture is not possible using these methods only.
Conclusion: *sustained efforts need to be continued in our endeavour to find a bone turnover marker as a diagnostic or prognostic tool for monitoring bone healing.*
Keywords :

Date of Submission: 16-09-2017 Date of acceptance: 05-12-2017

I. Introduction

Bone-specific alkaline phosphatase is a specific marker of osteoblasts and gives a good measure of bone forming activity.[1] The femur fracture appears to be a good model for studying fracture healing in clinical setting because of its frequency of presentation, the levels of bone-turnover markers produced and the incidence of delayed union.[1] The ability to detect the elaboration of specific molecular markers of cellular activity may complement the clinic-radiological methods by enhancing the accuracy of assessment of fracture healing and may also allow the early detection of fractures at risk of delayed or non-union.[1]Assessment of fracture healing is a subjective process without a readily available gold standard. Clinically and radiologically, fracture healing is defined as being delayed if the healing process has not beencompleted within 6 months[18]The development of a nonunion is a common complication following long-bone fracture. Its incidence ranges up to 46%,[18,20–24]depending on injury location, bone loss, soft tissue injury.[28] Till date, no clinical or scientific assessment can reliably predict successful fracture healing. The diagnosis of a nonunion is typically made by attentive clinicalexamination. [30] Radiographic scoring has been helpful, but not perfect, in predicting fracturehealing.[34] However, computerized tomography with reconstructed views still seems to be the most useful non-operator-dependent method for the evaluation of delayed or failed long bone union.[35]

. The measurement of bone turnover markers (BTMs) in serum quantitatively assesses the rate of bone remodelling and thus could be a valid tool for monitoring changes of bone formation. The markers can represent bone formation, matrix breakdown, and enzymatic activity of bone cells[39]. Alkaline phosphatase is a marker elevated in all mineralizing tissues..[40] High ALP levels and an increased rate of matrix production are found in cartilage prior to matrix calcification.[42,43]the bone isoenzyme of ALP (BALP) is considered a more specific maker of bone formation. The ideal marker would have no short- term biological variability (i.e., stable over at least several days or weeks). The assay would be simple and automatable. The assay should have a high sensitivity as well as specificity. An individual's rate of remodeling may vary over time.[2] The day-to-day variation is ~10% for formation markers and 20% for resorption markers.. Bone resorption markers respond faster than formation markers to changes in bone remodeling because of shorter time of resorption than formation.[2] So the aim of the study was to evaluate the changes in serum alkaline phosphatase levels during healing of isolated femur shaft fractures treated with close reduction and interlocking nail

II. Materials And Methods

Adescriptive, prospective and follow up studywas conducted in the department of Orthopaedics, SMS Medical College & Attached Hospitals, Jaipur (Rajasthan)from Januaryto December 2015..A sample size of 64 patients 18-45 year,of isolated simple, fresh (< 7 days), traumatic,closed fracture of shaft of femur, treated close reduction and interlocking nail femur in young adults was studied.Isolated simple closed fracture of shaft of femur bone managed as close reduction and interlocking nail femur.Traumatic fractureFresh (< 7 days) fracture, with Patient giving informed consent for study. Associated head injury or polytrauma case, Alcoholism,Drug abuse, Pathological fracture,Metabolic bone diseases,PeripheralNeuropath,Inflammatoryarthritis,Diabetes mellitus uncontrolled, Malignancy,Patients on medications including (steroids, anticoagulants, bisphosphonates,antiepileptics, calcium, fluorides and immunosuppressive drugs),Chronic liver disease,Chronic renal failure Pregnant or lactating female were excluded.

The routine investigations including haemogram, blood glucose level, liver and kidney function tests were done to exclude any factor effecting fracture healing, relevant radiographs with other preoperative investigations were obtained. The case record form was filled and an informed consent was taken. All the patient were treated as internally fixed using interlocking nail with 2 distal and 2 proximal locking bolts. Early range of motion exercises were started at knee and hip joint on the first post-operative day and patient was mobilized with help of crutches.

Sample size calculated as 80% study power and α error 0.05, assuming standard deviation of 40 in the mean serum alkaline phosphatase level found in a pilot study conducted on 5 patients. For Biomarker Examination2 ml. of peripheral blood will be collected in EDTA coated vials under standard aseptic technique.Quantitative determination of serum ALP (Alkalinephosphatase) activity (at ph 10.4, temp. 37^0c was donespectrophotomatrically(405mm)usinan p-nitrophenyl phosphate as a substrate and other reagent provided by LABKIT, according to LABKIT manual.Reference range of normal adult is between 25-140 IU/L at 37°C.Follow up will be done on the day of admission, 14^{th} day, 21^{st} day, 1 month, 42^{nd} day, 2 month, 3 month day counted from day of trauma and last sample was collected when serum alkaline phophataselevelreturned to in its normal rangeThe patients were followed up clinically for the signs of fracture union that is pain and tenderness at the fracture site at 0 + 4 week then every month till 9 months.The fracture union was defined as the time when three of the four cortices showed bridging callus across the fracture site. An antero-posterior and a lateral radiographs weretaken to assess the fracture healing. The radiographs were taken at 0 wks(at the time of presentation),On the day of surgery then 4 wks, 8 wks, 12 wks, 16 wks, 20 wks, 24 wks, 28 wks, 32 wks and 36wks.The presence or absence of callus and the number of cortices bridged by callus were observed in each radiograph and documented in case record sheet.Non-union is defined as the cessation of all reparative processes of healing without bonny union. A fracture that at minimum of 9 months post occurrence and is not completely healed which is the case of group B_2 and has not shown radiographic progression for three months is labelled as non-union of diaphyseal fracture of femur bone.Quantitative determination of serum ALP (Alkalinephosphatase) activity (at ph 10.4, temp. 37^0c will be done spectrophotomatrically (405 mm) using an p-nitrophenyl phosphate as a substrate and other reagent provided by LABKIT, according to LABKIT manual.Reference range of normal adult is between 25-140 IU/L at 37°C.This regent kit is intended for "in vitro" quantitative determination of Alkaline Phosphatase activity in serum/plasma.

III. Sample Required

Unhaemolysed Serum, heparinized plasma/ EDTA plasmain Children 3-15 years104-390 IU/l and ≥ 18 yearsAdults25-140 IU/l was the reference range.

Statistical Analysis: was performed with the SPSS,Trial version 20 for Windows statistical software package (SPSS inc., Chicago, il, USA) and PRIMER. The Categorical data were presented as numbers (percent)

and were compared among groups using Chi square test. Groups were compared for demographic data were presented as mean and standard deviationand were comparedusing by student t-test and ANOVA for more than two groups Test applying to find out the most significant groups among all the groups. The serum level of alkaline phosphatase were compared at different follow up of post injury from baseline by using Wilcoxon sign test and paired t-test (for paired analysis) Probability P value <0.05 was considered statistically significant

IV. Observations And Results

All theSixty four patients were followed up for 9 months with no lost to follow up , whose age ranged from 18 - 44 years (28.17 ± 6.939 years). The maximum proportion (46.88%) was observed in18-26 years of age groups.According to mean age,the mean age of group A was 28.02±7.07 and in group B_1 was 26.50±5.03 and in group B_2 mean age was 34.20±8.38.(P=0.09N) Out of 64 patients, 51 patients were male and 13 patients were female, The M:F ratio was 3.92:1 . In group-A females were 17.78% and male were 82.22%, in Group B_1, females were 21.43% and male were 78.57% and group B_2 female were 20% and male were 80%,;P = 0.952In the study, the most common mode of injury was road traffic accident (92.19%), other modes were Slip &Fall(3.13%) and fall from height (4.69%).In Group B_1 78.57% and in Group A 95.56% were from RTA. No significant difference were observed according to mechanism of injury among the groups. The maximum proportion (75%) was observed in Middle 1/3 followed by (20.31%) in Lower 1/3 and least (4.69%)were in upper 1/3.Transverse pattern were more in all the groups followed by oblique than spiral type. No case were observed of spiral type in group B_2.The common side were right in 59.38% .Overall right side cases were more in group-A and Group B_2, while in Group B_1 both side cases were equal in numbers.

Upto at 8 weeks following injury pain and tenderness was present at fracture site in all of the cases. At 4, 5,6,7 months post injury tenderness at fracture site were 45 (70.31%),25 (29.69%)19 (29.69%) 11 (17.19%) casesand 8^{th} and 9^{th} months post injury tenderness at fracture site was present in only 5(7.81%) patients. We evaluated the level of ALP in the above 3 groups of patients based on absence of presence of tenderness. The levels of ALP were found to be higher in the group with presence of tenderness

In radiological **a**ssessmen**t**Bridging callus in 3 or more cortices across the fracture site was visible in 56 patients at 8 weeks post injury, it was discernable in 61 patients at 12 weeks post injury, whereas it was seen in all patients at 4 months. At 12 weeks 3(4.68%) patients had bridging callus seen in 3 or more cortices whereas 61(95.3%) patients had bridging callus in <3 cortices. At 16 week 21 (37.5%) patients had bridging callus seen in 3 or more cortices whereas 43(67.18%) patients had bridging callus in <3 cortices. At 24 weeks 45 (70.31%) patients had bridging callus seen in 3 or more cortices whereas 19(29.68%) patients had bridging callus in <3 cortices. At 9 months 59(92.18%) patients had bridging callus seen in 3 or more cortices whereas 5(7.81%) patients had bridging callus in <3 cortices. So these 5 patients labeled as non union and 14 patient who developedbridging callus in 3 or more cortices between 24 to 36 weeks labeled as delayed union. The maximum proportion 45 (70.31%) was observed in group A(union) followed by 14 (21.88%) ingroup B1 (delayed union)and least5(7.81 %)were in group B_2(non –union)The bony healing occurred at 4.56 ±0.76months (range 3 to 6months) in group A and at 7.29±0.47 months (range 7 to 8 months) in group B_1 and this was statistically significant. (P<0.001S) In group B_2 all five cases were from non-union in the follow up duration of healing.

There was no change at baseline in ALP level but mean ALP was significantly more in group A as compareed to group B_2upto seven months. But at 8^{th} and 9^{th} months no significant difference was observed In the group A with delayed union, the levels of ALP hadincreased from the baseline and reached themaximum level at 21^{st} day then decreased graduallyand similar pattern also followed by group B_1 but levels of ALP were loweredthan group A. But through the follow up period no significant rise was observed in group B_2. The mean difference was significantly more in group A as compared to group B_1 but no significant rise was observed in 7 and 8 months of follow up between A and B_1 and no significant rise was observed in Group B_2.

The mean value of serum ALP in group A at baseline was 83.64$\pm$17.21 IU/L and rose significantly (P<0.0001S) to a mean value of 239.78$\pm$37.92 IU/L at 14^{th} day. The level reached maximum 353.29$\pm$40.59 IU/L at 21st day which is significantly increased from baseline (p=0.001) when compared to that of time of injury. In Group A mean serum ALP were found to be significantly elevated even till 04 months. At 5 month the level of serum ALP had a mean value of 102.96 which was not significant from the baseline.

Significantly higher mean was observed in most of follow up period in group B_1 except in 7 month and 8 month of follow up from the baseline. In group B1The changes in mean serum ALP level in group B_2 were never significant and remained within normal limits throughout followup, so in our study total 64 patients were enrolled and studied which were allocated in group A (N=45), group B_1 (N=19) and group B_2 (N=5), depending on the progression, duration and type of bone healing. The average age of group A was 28.02$\pm$7.07 years and Group B_1 was 26.50$\pm$5.03 years and in group B_2 mean age was 34.20$\pm$8.38 years. The difference between the mean age of these group was not significant. The bonny healing occurred at 4.56 month (range 3 to 6 months) in group A and 7.29 (range 7 to 8 months) in group B_1 and this was statistically significant. In group B_2 all 5 cases were from non-union till the follow up duration of healing.

V. Discussion

In this study, adults of age group 18-45 years have included as the level of serum alkaline phosphatase varies with age. Majority of patients were males. In an injurydatabase[131] it was seen that 70% of injury death and over half of non fatal injuries occur among males with the largest male-to-female ratio (over four-fold) seen among adolescents and young adults.Female sex appeared to be a further risk factor for delayed healing in one of the studies.[31]In the present study 92% of the injuries were attributable to road traffic accidents. Adolescent and young adults are particularly at a high risk of injury due to RTA.[132]Their rates of death, hospitalization, and emergency department visits are approximately twice the rate for all ages combined.We considered road traffic accidents and fall from height are as high energy injuries when compared to household injuries which were considered as low energy injuries. In our study 96% of the injuries were high energy injuries while 4% were sustained by low energy trauma.

In this study for successful union in the femur the following criteria must be observed,The absence of pain and tenderness at the site of fracture and visible bridging callus across the fracture on plain radiography. In the clinical follow up during the study all the 59 patients demonstrated clinical signs of fracture union within the study period of 36 weeks. 5 patient demonstrated tenderness at the fracture site at 36 weeks. Thus 59 fractures clinically within the 36 weeks period and 5 fractures not healed clinically within 36 week of period. Hence these 5 fracture labeled as non union.

VI. Radioloical Outcome

In our study ,atthree months number of radiological union was 03 while number of clinical union (no tenderness at fracture side) was 09. In same manner at 4 month and 5 month number of patients having clinical union are higher than number of radiological union. It shows that radiological healing lags behind clinical assessment of fracture healing.

VII. Biochemical Assessment

Alkaline phosphatase is a marker of bone formation and the significantly raised levels of serum alkaline phosphatase at 14^{th}, 21^{st} and 28^{th}day 3 month after fracture signify the increased osteoblastic activity occurring at the fracture site. There was no statistically significant difference in the levels of the marker with patient characteristics such as age, sex, and injury factors like the mode and severity of injury, level and pattern of the fracture and presence or absence of comminution in fracture. The rise in levels of the marker was in agreement with various previous studiesby Nyman et al[106], Leung et al[108],

Bowles et al[109],Ingle et al[111,112]andHerman et al[120]. However the serial measurements in our study differed from that ofVeitchet al[122],in our study the levels peaked between 8 and 12 weeks whereas in the study by Veitch et-al the levels peaked at 24 weeks.In our study the mean serum ALP level remained within normal limits in all included patients at the time of admission. The variation in serum ALP level followed the same pattern in Group-A and B1, reaching a maximum level at 3^{rd} week in both groups .Serum ALP level remained elevated significantly till 4 months in Group-A and reached within normal limit when clinico-radiological union occurred. In Group B_1 mean serum ALP remained significantly elevated till 6 months. Till bony union occurred in Group A, at every interval the mean value of serum ALP of group A were significantly higher than of group B_1. The changes in mean serum ALP level in group B_2 were never significant and remained within normal limit till 9 months.Depending on the clinico-radiological parameters of progression of fracture healing, all 64 patients were allocated into two groups by the end of active follow up; Group A (n=45) clinico-radiological union achieved before or by the end of six months; and Group B (n=19) clinico-radiological union not completed by the end of six months. The Group B was further subdivided into B_1 (n=14); clinico-radiological healing not completed by six months but completed by the end of nine months, and B_2 (n=05) clinico-radiological healing not achieved even by the end of nine months- Non-union. the determination of serum ALP levels during fracture healing could be an additional tool in predicting fractures at risk of healed/ non-union of simple diaphyseal fractures, adding the clinician to prefer the early appropriate intervention at appropriate period.

The outcome of this study is that estimation of serum alkaline phosphatase correlates with the clinico-radiological signs of fracture healing in femur diaphyseal fracture. There is a significant rise in the level of the bone formation marker demonstrating an increased osteoblastic activity. The radiographic detection of callus also correlates with the level of serum alkaline phosphatase suggesting its role in the mineralization of the callus and consolidation of the fracture.The bone turnover markers are suggested as a non-invasive aid for monitoringfracture healing. They may help in the monitoring of fracture healing, complementing the clinico-radiological evaluation.Further studies in this direction can throw more light on the complex process of bone healing and the delicate balance between bone formation and resorption. Analyses of the volume of callus that is formed across the fracture site in combination with clinical signs of union remain the gold standard for monitoring fracture healing. But early detection of a slow healing or a non healing fracture is not possible using these methods only.[2]

Radiological features lag behind clinical assessment of fracture healing. Delayed diagnosis of a nonunion is costly from both the patient and treatment standpoints. The complex mechanisms and the mysterious pathways of a bone not healing normally need to be revealed as the secret of predicting which injured bone will not heal lies within them. Therefore, sustained efforts need to be continued in our endeavour to find bone turnover markers as diagnostic or prognostic tools for monitoring bone healing.

Hence there is a need to develop an accurate, precise, reliable, reproducible, patient-doctor friendly and post-detective method to measure fracture healing objectively. Skeletal turn-over can be assessed easily and non-invasively by the measurement of turn-over markers. Thus, early knowledge of the individual progress of fracture could help to keep of delayed or non-union by enabling modification of the host biological response.In adult patients under the ideal circumstances the expected time of bone-union of an uncomplicated diaphyseal femur fracture is approximately 4 to 8 months which is the case of group-A (mean union at 4.56 months). Delayed union is considered as a fracture that requires more time for complete bone union than the usual but will unite ultimately, which is the case of group B_1 (mean union of 7.29 months).In the present study the incidence of clinico-radiological non-union at the end of 9 months was 7.8%. In our study the serial serum ALP levels were correlated with the clinico-radiological progression of bonny fracture healing in all patients. In all 64 patients we were able to credit the fate of fracture healing process by the serial estimation of serum ALP level. We observed that serum

ALP level at 3rd week was correlated with future outcome of these fractures. We may predict the future outcome of these fractures at as early as 3rd week. Our findings were related with ALP level variation during fracture healing were corresponding with that of other studies.In our study, changes in serum ALP level in group A and B_1paralleled the process of fracture healing as documented by clinico-radiological evidences. Though, in group A, mean ALP returned to normal reference limits by clinico-radiological fracture healing, in group B_2 these levels remained elevated till six months. Suggestive of ongoing osteoblastic activity in these patients. At six months clinico-radiology it was not evident that which patients will fall into delayed union and which one will be in non-union. Waiting 9 months to diagnose and treat a non-union is patentlyunreasonable in modern world. These dilemma raised a question that whether a clinician should wait for radiological sign to settle down for an establish diagnosis of non-union or one can predict and can intervene early by observing a biomarker, like serum ALP.We may predict the future outcome of these fractures as early as 3rd week by observing the serum ALP level.

VIII. Limitations of the study

1. The number of patients was limited in this time bound study.
2. The periodic longitudinal estimation of bone turnover markers for assessing fracture healing till consolidation and remodeling could not be carried out due to the fixed time period and the limited financial resources available.Other Bone turnover markers have not been considered due limited financial resources available.

IX. Conclusion

The bone turnover markers are suggested as a non-invasive aid for monitoring fracture healing. They may help in the monitoring of fracture healing, complementing the clinico-radiological evaluation.

Table No 1: Baseline Charactorstics Of The Study Population

	Group A(N=45)	**Group B1**(N=14)	**Group B2(N=5)**	**Total**	**P Value LS**
Age Group	No	No	No	No	
18 To 26	21(46.67%)	8(57.14%)	1(20%)	30(46.88%)	
27 To 35	17(37.78%)	6(42.86%)	2(40%)	25(39.06%)	
36 To 45	7(15.56%)	0	2(40%)	9(14.06%)	0.23NS
Sex					
F	8(17.78%)	3(21.43%)	1(20%)	12(18.75%)	
M	37(82.22%)	11(78.57%)	4(80%)	52(81.25%)	0.95NS
Mode Of Injury					
Fall From Height	1(2.22%)	2(14.29%)	0	3(4.69%)	
RTA	43(95.56%)	11(78.57%)	5(100%)	59(92.19%)	0.29NS
Slip & Fall	1(2.22%)	1(7.14%)	0	2(3.13%)	
Oblique	17(37.78%)	6(42.86%)	3(60%)	26(40.63%)	
Spiral	7(15.56%)	2(14.29%)	0	9(14.06%)	
Transverse	21(46.67%)	6(42.86%)	2(40%)	29(45.31%)	0.842NS
Location					

Lower 1/3	10(22.22%)	2(14.26%)	1(20%)	13(20.31%)	0.438NS
Middle 1/3	34(75.56%)	11(78.57%)	3(60%)	48(75%)	
Upper 1/3	1(2.22%)	1(7.14%)	1(20%)	3(4.69%)	
Side Wise					
Left	14(31.11%)	7(50%)	2(40%)	26(35.94%)	0.009S
Right	31(68.89%)	7(50%)	3(60%)	38(64.06%)	

Table No 2: Fracture charactorstics among the groups

Level of fracture	**No. of patients(N=64)**	**Percentage(%)**
Upper 1/3	3	4.69
Middle 1/3	48	75.00
Lower 1/3	13	20.31
Level of fracture	No. of patients	%
Transverse	29	45
Oblique	26	40
Spiral	9	15
Side		
Left	23	35.94
Right	41	64.06

Table No3: Comparison Between Radiological And Clinical Signs Of Fracture Healing Among The Groups

Tenderness	**On day of operation**	**1 m**	**2 m**	**3 m**	**4 m**	**5 m**	**6 m**	**7 m**	**8 m**	**9 m**
Present	64	64	64	56	34	21	19	10	5	5
Percentage %	100	100	100	87.5	53.12	32.81	29.68	15.62	7.81	7.81
No. of cortices in bridging callus										
0		64	8	3	1	0	0	0	0	0
1		0	40	19	5	5	3	2	2	2
2		0	16	39	37	18	16	7	3	3
3		0	0	3	21	37	31	41(10 New)	37(4 New)	33
4		0	0	0	0	4	14	14	22	26
No. of 3 < cortices in bridging callus										
Visible		0	0	3	21	41	45	55	59	59
Not visible		64	64	61	43	23	19	9	5	5

Biochemical Monitoring

Table No 4: Serum Alkaline Phosphatase (ALP)at different time interval

	DOA	**14th day**	**21st day**	**1 month**	**42nd day**	**2 month**	**3 month**	**4 month**	**5 month**	**6 month**	**7 month**	**8 month**	**9 month**
N	64	64	64	64	64	64	64	61	42	23	19	9	5
Mean	82.14	219.16	317.72	290.09	249.64	208.48	163.14	126.97	109.55	106.17	86.79	79.11	77.00
Std. Deviation	15.45	55.24	81.38	73.50	63.98	51.47	44.27	38.34	32.57	24.82	13.70	9.62	4.90
Median	81.50	226.00	340.50	308.00	261.00	208.00	173.00	128.00	108.00	98.00	84.00	80.00	79.00
Minimum	51	76	82	80	78	77	54	66	54	72	61	66	71
Maximum	119	318	420	396	367	318	247	196	176	146	119	92	83

Figure: 1Distribution Of Cases Among The Groups According To Mean Difference In ALP From Baseline At Different Interval Of Follow Up

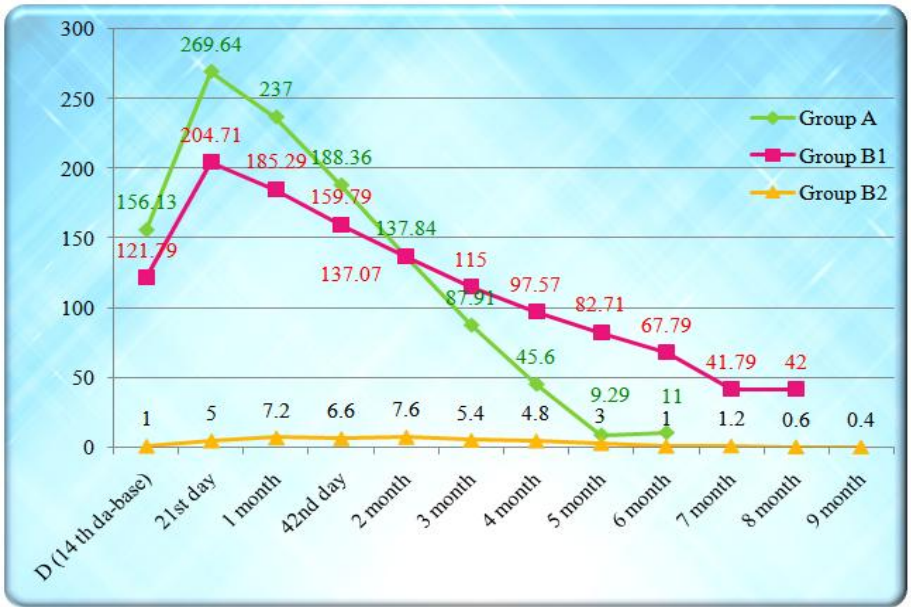

Table No. 5 Serum Alkaline Phosphatase (ALP) At Different Time Interval Of Injury Among The Groups

Group		DOA	14th day	21st day	1 month	42nd day	2 month	3 month	4 month	5 month	6 month	7 month	8 month	9 month
A	N	45	45	45	45	45	45	45	42	24	4			
	Mean	83.6	239.8	353.3	320.6	272.0	221.5	171.6	131.0	95.4	94.3			
	SD	17.2	37.9	40.6	40.9	43.1	39.5	33.6	33.7	24.7	20.9			
B1	N	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	4.0	
	Mean	79.8	201.6	284.5	265.1	239.6	216.9	194.8	177.4	162.5	147.6	99.86	89.00	
	SD	10.8	30.8	32.9	27.7	30.1	24.0	17.0	10.7	8.8	6.1	29.44	7.62	
B2	N	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5	5
	Mean	78.2	79.2	83.2	85.4	84.8	85.8	83.6	83.0	81.2	79.2	79.4	78.80	78.60
	SD	1.3	3.0	2.8	7.3	7.0	7.9	7.2	5.6	7.3	5.9	5.0	5.630	2.510
P value LS		0.59NS	<0.001S	<0.001S	<0.001S	<0.001S	<0.001S	<0.001S	<0.001S	<0.001S	<0.001S	0.14NS	0.053NS	NA

Table 6: Distribution of cases among the group according to ALP at different interval of follow up from baseline

	Group A(N=45)				Group B1(N=14)				Group B 2(N=5)			
Group from Baseline	**N**	**Mean**	**SD**		**N**	**Mean**	**SD**		**N**	**Mean**	**SD**	**P Value LS**
	45	83.64	17.21		14	79.79	10.81	<0.001S	5	78.2	1.3	0.51NS
14th day	45	239.78	37.92	<0.001S	14	201.57	30.84	<0.001S	5	79.2	3.03	
21st day	45	353.29	40.59	<0.001S	14	284.5	32.9	<0.001S	5	83.2	4.77	0.053NS
1 month	45	320.64	40.87	<0.001S	14	265.07	27.74	<0.001S	5	86.4	7.23	0.062NS
42nd day	45	272	43.06	<0.001S	14	239.57	30.13	<0.001S	5	84.8	6.98	0.07NS
2 month	45	221.49	39.5	<0.001S	14	216.86	24	<0.001S	5	85.8	7.89	0.06NS
3 month	45	171.56	33.56	<0.001S	14	194.79	16.99	<0.001S	5	83.6	7.2	0.09NS
4 month	42	131	33.69	<0.001S	14	177.36	10.66	<0.001S	5	83	5.61	0.09NS
5 month	24	102.96	20.67	0.053NS	14	162.5	8.78	<0.001S	5	81.2	7.26	0.39NS
6 month	4	94.75	19.48	0.22NS	14	147.57	6.07	<0.001S	5	79.2	5.93	0.72NS
7 month					14	100.64	29.38	0.051 NS	5	79.4	5.03	0.61NS
8 month					4	89	7.6	0.134 NS	5	78.6	5.77	0.88NS
9 month									5	77	4.9	0.611NS

*Dr. Anand Prakash. "Serum Alkaline Phosphatase, A Prospective Biomarker For Assessment of Progress of Fracture Healing." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) , vol. 16, no. 12, 2017, pp. 27–33.