A Review on the Article: Role of Common Biochemical Markers for the Assessment of Fracture Union

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Abstract Criterion for patient selection and demographic comparison between the two groups, the numbers in individual groups (normal union or defective union) how the observers were blinded for the samples and control group measurements in the graphs were not mentioned. No data on actual measurement levels is given. No where it is mentioned like it is an average of all normal union or defective union in tables or diagrams. The treatment methodology maybe still focused including either conservative or surgical treatment since a displaced fracture cannot be compared with an osteotomy. The cases shall be followed up for a longer period. Some suggestions on how to blind the observers is given. In the one year period there was neither mention of the failure of treatment or complications of any of neither these 36 cases nor any drop out for follow-ups. There was also no mention of any case which initially put on conservation was changed to surgical management. The authors could have one group of patients taking this food stuff and another group who refused this food stuff. The statistical test used to compare the levels of factor is not mentioned. Mere statement that '*p*' values were significant will not benefit the reader. Failure to produce X-rays even for a single case weakens the study. X-rays are needed to confirm the diagnosis of a fracture and confirm the position of implants and fracture fragments. The remaining period after confirming the fracture/implant position the case shall be followed only with marker estimation. Once the desired levels of increase or tapering of marker level achieved then X-rays can be taken to correlate with clinical findings and radiology. Union as

one group and the second group shall be called as non-union or delayed union. The second group (the poor callus group) is mentioned as malunion possibly by over-sight. Probably they were meaning the non union or delayed union group or defective union as malunion. This should be preferably be written non union or delayed union. Malunion means the fracture actually unites and union process is completed. In a group of fractures (hypertrophic non unions) the callus formation is excessive, still the fracture is ununited. Thus the enzyme or markers alone cannot disclose the details of the completion of union they can herald bone formation.

Keywords Blinding · Marker estimation · X-rays · Non-union · Malunion

I read the article 'Role of common biochemical markers for the assessment of fracture union' [1] with great interest. I would like to congratulate the authors for an excellent work. I would like to make the following comments on this paper.

In the abstract there is no mention of the control group of healthy subjects which is mentioned in the main article. Only comparison between two groups was either the fracture was uniting or not uniting.

This study was intended to be a randomized case control study. However clear exclusion criterion for patient selection and demographic comparison between the two groups were found wanting. The authors mention that in the 36 cases they studied, those cases that went for normal union had a pattern of Alkaline Phosphatase and Urinary Hydroxy Proline level during the period of treatment. Also they mention the fractures that did not proceed to unite had a pattern of Alkaline Phosphatase and Urinary Hydroxy Proline levels during the

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period of treatment. Till the very end the authors have not mentioned the numbers in individual groups (normal union or defective union) n_1 and n_2 . This is very important to deduce what is the percentage of defective union in the sample population, for example in the United States the percentage of non unions in fractures is 2–10 % [2].

There is no mention how the observers were blinded for the samples. i.e., whether periodic results of the biochemical analysis were known to those who observe radiological healing in X-rays or not till the final stage of completion of the study. There is a good chance of bias in interpretation of radiographs. There is a chance of bias if the worker who does the clinical assessment has the knowledge as to which case showed radiological union. Thus it becomes important if the samples blinded till the end of this study.

No where one could see the mention of control group measurements in the graphs. The authors have not mentioned all real biochemical readings of at least one case. No data on actual measurement levels is given. No where it is mentioned like it is an average of all normal union or defective union in tables or diagrams. Only schematic diagrams or representations are given. This gives no details on the real setting of the study.

It appears that two groups of case (normal union or defective union) were formed out of all the cases (not to mention about the controls) after final result of union or defective union. Clinical data were not properly presented or analyzed. The details of bones that were fractured in each case, whether diaphysis (in the middle of the bone) or metaphysis (near the end of the bone) can be of use. This is because the fracture healing method and rate are different in these regions. These details were not mentioned.

With regard to age, only in one place in the article the authors mention 'adults'. The elimination of children from the group will reduce the significance of the study. Children can form a sub group of analysis. Instead including all age group will bring out a useful common result for all age groups. The treatment methodology maybe still focused including either conservative or surgical treatment. There can be at least a mention of which cases went for conservation and which cases had surgery. To be more precise a displaced fracture cannot be compared with an osteotomy. In short, no specific mention about how the fractures were reduced, fixed or treated from a clinical standpoint were there. The three cases of osteotomies could be studied separately.

The cases shall be followed up for a longer period, as the authors accept that patients need 200 days at least for the marker levels to reach a baseline [1]. This can be done for those patients who came for regular follow ups and are willing to co-operate for the research. If such patients can be explained the need for the follow ups in a medical college setting. The amount of blood for the factor study by

periodic venepuncture is not mentioned. Collecting of fasting blood samples and collecting of 24 h urine for analysis need either hospitalization or intelligent patients. This is a clinical and biochemical study. I find the biochemical part is well written and elaborate.

There is a chance of bias as to which case showed radiological union to those who assess the levels of Alkaline Phosphatase and Urinary Hydroxy Proline. There is no mention if the samples were blinded till the end of the study.

Separate blank tables provided in this article as Tables 1, 2, and 3 could have been maintained by different set of observers. These can be used to follow up individual cases for levels of Alkaline Phosphatase and Urinary Hydroxy Proline levels and radiological new bone formation. Only on completion of the entire study these three tables could be compared.

Next issue is the problem of drop outs and complications of the treatment. In the one year period (August 2008–July 2009) interestingly there was neither mention of the failure of treatment or complications of any of neither these 36 cases nor any drop out for follow-ups.

Were all the cases are exactly consecutive fracture cases for which the final treatment could be decided within a week? It is not understandable how will the authors know a particular case will be fit and can be operated within a week, that too on the first day of presentation? There can be more number of cases in reality and the authors could have left them out as these cases could not be operated. Or it can be those which cannot be operated were offered conservation.

There was also no mention of any case which initially put on conservation was changed to surgical management.

It is unethical to ask a patient who has fracture to not to take calcium supplements or collagen food stuffs. These are food stuffs that can augment fracture healing. Instead the authors could have one group of patients taking this food stuff and another group who refused this food stuff. It is unbelievable to monitor such things in out-patient set up. There is no mention as to how many patients were kept as in-patients throughout the study? Were some of them followed up as out-patients? Is it practicable to keep these patients even from smoking, leave alone controlling them from eating food stuff? One can only believe subjectively so. There is no mention of diabetes mellitus any where [3]. The statistical test used to compare the levels of factor is not mentioned. Mere statement that ' p ' values were significant will not benefit the reader.

Coming to the method of comparison, there is nowhere an example of an X-ray series taken for tracking healing was shown. Failure to produce X-rays even for a single case among 36 cases followed-up weakens the study. The series of X-ray views from one case of each group the

Table 1 Levels of alkaline phosphatase in all 36 patients

Patient	ALP on day of injury	Age of the pt	1st week	3rd week	8th week	12th week
1 to 36						

Table 2 24 h urinary hydroxy-proline levels for all patients

Patient	UHP on day of injury	Age of the pt	1st week	3rd week	8th week	12th week
1 to 36						

Table 3 X-ray appearances for all patients

Patient	Bone	Diaphysis/ metaphysis	Age of the pt	1st week position of fracture and new bone	3rd week position of fracture and new bone	8th week position of fracture and new bone	12th week position of fracture and new bone
1 to 36							

normal union and defective union can be produced with the corresponding level of factors below. Alternatively the curve of the factor levels can be plotted with side by side X-rays.

Routinely all 36 cases were subjected to 4 (1st, 3rd, 8th 12th weeks) $\times$ 2 views (AP and Lateral). This makes 8 X-ray views. It takes 1.56 μ Sv in an average for one view of leg [4]. It makes $1.54 \mu\text{Sv} \times 8 = 12.32 \mu\text{Sv}$ for one patient. The maximum allowable radiation dosage for individual organ for persons other than radiation worker per year is 50 μ Sv and for the lens it is 15 μ Sv per year and anything more than this will cause cataract [5]. Use of X-ray equipment is often not handy and the analysis unclear [6]. X-ray techniques have their limitation in minor fractures. Certain fractures and soft tissue structures make the analysis difficult. Detection of non-union and the need for surgical intervention is ignored or delayed [7]. The mere radiographic persistence of a fracture line does not invariably indicate non-union [8]. Instead after 50 % of work was over the number of X-rays could have been reduced. It is understandable that one set X-rays are needed to confirm the diagnosis of a fracture. It is also allowable to have one set X-rays after the procedure to confirm the position of implants and fracture fragments. The factors enzymes etc. can be measured periodically. At the end of the study an X-ray could have been taken to confirm union or defective-union. This is because the authors persist with the treatment irrespective of the X-ray picture. There is no mention of early callus or evolving callus anywhere for a claim that continuous X-rays are necessary. I feel the number of X-rays could be lesser. The remaining period after confirming the fracture/implant position the case shall be followed only with Alkaline

Phosphatase and Urinary Hydroxy Proline and other marker estimation. Once the desired levels of increase or tapering of Alkaline Phosphatase and Urinary Hydroxy Proline level achieved then X-rays can be taken to correlate with clinical findings and radiology. The authors claim that the factors estimation studies the events as they are happening. Similar opinions that radio logic appearance is a factor of past osteogenic activity in the tissue and not due to current histology is shared by other workers [9]. The author explains the fracture is healing in one group and not in the other. It cannot be said that all the cases will unite within the time frame mentioned. This study also does not tell about the end point of union, it can be useful in planning the intervention and not starting loading of the limb etc. In this study there cannot be an end point as such. The only thing that can be said is whether the new bone is formed or not.

One interesting observation was that it should be either union as one group and the second group shall be non-union or delayed union. The second group is mentioned as malunion possibly by over-sight. Malunion refers to deformity at the fracture site and not a problem of union process. The orthopedic surgeons in the authors will agree this. Throughout the article the authors have mentioned malunion for the poor callus group. Probably they were meaning the non union or delayed union group or defective union as malunion. This should be preferably be written non union or delayed union. Malunion means the fracture actually unites and union process is completed. It does not mean a defective fracture healing process. Callus formation will be good in both union and malunion. Callus formation will be less in non unions or oligo-trophic non unions. Callus or new bone may even be present in hypertrophic

Fig. 1 Radiograph of leg showing exuberant callus on either side of the fracture in tibia. The fracture is still ununited. This is hypertrophic non union

non unions (Fig. 1). There was no mention about this type of cases. In this group (hypertrophic non unions) the callus formation is excessive, still the fracture is ununited. Thus the enzyme or markers alone cannot disclose the details of the stability of union.

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