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Research Article

ASSESSMENT OF SERUM PARATHYROID HORMONE FLUCTUATION DURING FRACTURE HEALING WITH ORAL ADMINISTRATION OF DRUG *CISSUS QUADRANGULARIS* IN PATIENTS OF BONE FRACTURE

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ABSTRACT

This study gives an understanding about the PTH mode of action as it accelerates the natural fracture healing process by shrinking callus size and increasing degree of mineralization of the fracture callus; thereby restoring intrinsic material properties. But, in human beings very few clinical research studies has been conducted with help of Hormonal parameters and its fluctuation during fracture healing with use of Ayurvedic formulation. Based on this, a random controlled study was conducted and fracture healing was assessed in the patients with simple and single fracture with assessment parameter hormone PTH (parathyroid hormone) and resulting values were statistically evaluated during fracture healing. treated group shows elevation pattern of serum hPTH so early initiation of bone resorption with early initiation of osteoblastic activity and continuous up to bone maturation so hardening of callus at fractured site may also quicker and this may helps to reduction in healing period or immobilization period and so early rehabilitation is possible.

KEYWORDS: Fracture, *Asthishrunkhala, Cissus qudarngularis*, Parathyroid hormone, *Bhagna*.

INTRODUCTION

In present days the fracture healing is assessed subjectively along with various objective parameters like radiological, histopathological, mechanical, biochemical and hormonal parameters. Among these radiological, histopathological, mechanical methods are commonly followed by most of the researchers in assessing fracture healing and the other hormonal assessment methods used seldom in comparison. Animal study demonstrates that parathyroid hormone accelerates natural fracture healing process in the femoral osteotomy model at Department of Orthopedic Surgery, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Miki-cho, Kita-gun, and Kagawa, Japan.[1] This study gives an understanding about the PTH mode of action as it accelerates the natural fracture healing process by shrinking callus size and increasing degree of mineralization of the fracture callus; thereby restoring intrinsic material properties. But, in human beings very few clinical research studies has been conducted with help of Hormonal parameters and its fluctuation during fracture healing with use of Ayurvedic formulation. Based on this, a random controlled study was conducted and fracture healing was assessed in the patients with simple and single fracture with assessment parameter hormone PTH (parathyroid hormone) and resulting values were statistically evaluated during fracture healing.

Parathyroid hormone[2] Human parathyroid hormone (hPTH)) is an 84 amino acid residue peptide it is a major physiological regulator of phosphocalcic metabolism. hPTH increases serum calcium concentration by its action on kidney (enhancing tubular ca^{++} reabsorption and phosphate excretion) and bone (stimulating osteoclastic activity and bone resorption). It indirectly affects intestinal absorption of ca^{++} by stimulating renal 1alpha hydroxylation of 25 hydroxyvitamin D. The release of PTH is controlled by the serum concentration of ca^{++}. The measurement of intact PTH correlates best with the hormone production and biological activity. Low-dose hPTH triggers cyclic AMP-dependent protein kinase in some populations of bone cells bearing PTH receptors, which stimulates the proliferation of osteoblasts.

***Cissus quadrangularis* & Fracture Healing**

Studies on fracture healing suggest that this unidentified anabolic steroid may act on estrogenic receptors of the bone. Efficacy of *Cissus quadrangularis* on early ossification and remodeling of bones have been reported and it has been observed that *Cissus quadrangularis* acts by stimulation of metabolism and

increased uptake of the minerals calcium, sulpher and strontium by the osteoblasts in fracture healing.[3] *Cissus quadrangularis* is found to contain vitamins and steroids, which are found to have specific effect on bone fracture healing. The anabolic steroidal principles from *Cissus quadrangularis* showed a marked influence in the rate of fracture healing by influencing early regeneration of all connective tissues involved in the healing and quicker mineralization of callus.

Purpose: Though, the drug *Cicccus Quadrangularis* is being used in fracture healing since days of Samhitas. The action of drug in accelerating the process of bone healing was not explored on objective evidences. Hence, the study was undertaken with the purpose, 'to explore the physiological impact of *Cicccus Quadrangularis* and ultimately on the process of bone healing in terms of parathyroid hormone fluctuation'

METHODOLOGY

Aim: To evaluate the effective remedial therapy for acceleration of fracture healing so as to Rehabilitate the individual as early as possible.

Objective

To correlate the serial values of parathyroid hormones during process of fracture healing.

Study design

Study Type : Interventional
Purpose : Treatment
Control : controlled
Timing : Prospective
No. of Groups : Two
Sample Size : 40 in each group (Total=40x2 i.e. 80)

Inclusion Criteria

1. Patients of single bone fracture with good general condition.
2. Males or non pregnant females aged 12 to 70 yrs.
3. Able to communicate adequately with the investigator and to comply with the requirements for the entire study.
4. Capable of and freely willing to provide written informed consent prior to participating in the study.

Exclusion Criteria

1. Patients of systemic disorders like DM, PTB, malignancy
2. Patients of thyroid dysfunction history
3. Patients of calcium disorder
4. Patients of open fracture and fracture with dislocation & who requires acute medical care and surgical interventation.
5. Patients below 12yrs and above 70yrs.
6. Immunocompressive patients
7. Highly Displaced fracture which needs anesthesia to reduce.
8. Pregnant / Lactating women.
9. Patient on steroids, oral contraceptive pills or estrogen replacement therapy.
10. Alcoholics and/or drug abusers.
11. Patients suffering from major systemic illness necessitating long term drug treatment (Rheumatoid arthritis, Psycho-Neuro-Endocrinal disorders, etc.)
12. H/o hypersensitivity to any of the trial drugs or their ingredients.
13. Patients who have completed participation in any other clinical trial during the past six (06) months.
14. Any other condition which the Investigator thinks may jeopardize the study.

Drug interventions

For Group A (Treated group)	For Group B (controlled Group)
1.Drug - *Asthishrunkhala churna*	1.Drug-Starch (placebo therapy)
2. Dose – 10 gm per day in three divide doses	2.Dose – 500mg
3. Route of administration – orally	3. Route of administration – orally,
4. Vehicle – Luke warm water	4. Vehicle – Luke warm water
5. Duration- 30 days.	5. Duration- 30 days.

General management of fracture

It includes Immobilization of the part i.e.post cast and POP. Post cast on day 1st, POP on 7th day. For trial group (A) Anti-inflammatory analgesic drugs are avoided because drug *Ciccus qudrangularis* has anti-inflammatory analgesic property. Patients in **Group-A** who required medication for further complications they are excluded from study with proper advice and care. Patients of **Group-B** for pain plain paracetomol/Diclofenac sodium is given if needs and separate documentation was maintained. Patients were advised to follow-up on Day 07, 21& day 31 to assess parameters.

Assessment parameter (Objective)

1. **Hormone** – parathyroid hormone is assessed on Day 1st, 7th, 21st& 31st day.

Methods of assessment

Prior to selection (Screening)

1. Informed Consent /Assent
2. Eligibility evaluation
3. Laboratory investigations

During Selection (Baseline)

1. General information- (Personal Identification and Demographic profile)
2. Medical history, General Physical and Systemic examination
3. Clinical Assessment by fracture Symptoms and radiograph.
4. Issue of drugs and drug compliance report form
5. Instructions to come on next visit

During Treatment i.e. on 7th, 21st, 31st

1. Assessing drug compliance
2. Physical examination
3. Laboratory investigations (Serum PTH)

4. Issue of drugs and drug compliance report form

Statistical analysis

Hormone parameter presented as mean ± SD. Categorical variables were expressed in actual numbers and percentage. One way repeated measure ANOVA test was performed to compare the Serum parathyroid hormone at different points in each group. Changes in these variables at different time point between two groups were compared by wilcoxan rank sum test (Mann–Whitney test). STATA version 10.0 was used for statistical analysis.

Data Management: A case report form (CRF) for each patient in trial is prepared to note down all clinical observations. The data is handled in a way to maintain confidentially and ensure accuracy. Efforts were made to maintain error free records.

Ethics: Institutional Ethics Committee: after ethical approval for study from IEC work was initiated and the final study report is also presented before the Institutional Ethics Committee(s) for approval. All amendments suggested by EC(s) are implemented and letter of pre & final approval of institutional ethical committee enclosed in annexure.

OBSERVATION, RESULTS & DISCUSSION

Total 96 patients were screened for study. Out of them 12 patients are excluded with proper referral as they did not fit in inclusion criteria, whereas 04 patients are withdrawn from study due to protocol voidance with irregular follow-up. They were advised for alternative treatment. 80 patients were enrolled and taken-in for the trial assessment in the study. They were divided into two groups with simple random allocation method, Group A (Treated Group)- treated with *Asthishrunkhala* capsule orally. Group B- (Control group) treated with placebo Starch capsule. Observations were made during and after the treatment, to find out the fracture healing acceleration property of drug *Ciccus quadrangularis* in terms of Serum parathyroid fluctuation**.**

The observational details regarding the incidence factors pursue as follows: Out of the 80 patients, maximum 18 (22.5%) patients were in 31-40 yrs age Group. thereafter 16 (20%) patients in age Group 41-50 yrs and patients in age Group 51-60 yrs are also 16 (20%). patients are in above 60 years age Group were 09 (11.25%) and patients were in 21-30 years age Group were11 (13.75%) and 10 (12.5 %) patients were in 12-20 years age Group. According to the observations noted- it is evident that a maximum patients inflicted by fractures were seen in 31-40 years age group and the most common cause is the vehicular accident and second cause is fall which is common in aged group. This observation correlates the international prevalence of fracture and musculoskeletal injuries.[4]

Regarding the incidence in genders, Out of 80 patients, 46 (57.5 %0 patients were male & 34 (42.5%) patients are female. Male: Female ratio in the study was found out to be 60:50 the ratio regarding the incidence of fracture in between the sexes is found to be relatively insignificant. According to observation done regarding occupation of patients- it was found that Out of 80 patients under study 13 (16.25 %) patients were working in private sector. 04 (5 %) patients were working in govt. sector.11 (13.75%) patients were working in own business. 05 (6.25% patients were labors by occupation. 14 (17.5%) patients were taking education. 06 (7.5%) patients are retired & 27 (33.75%) patients are Housewife by occupation Thus, it can be said that most sufferers are those who are engaged in daily outdoor activities. Regarding the bone being involved in the fracture, it was observed that amongst the 80 patients under the trial study- a maximum Numbers of 17 patients (21.25 %) were inflicted with fracture of the phalanx followed by fractures of radius – 16 in number (20 %), 05 patients (6.25 %) were inflicted with fracture of the Humerus bone, 09 patients (11.25%) were inflicted with fracture of the Metatarsals, 08 patients (10 %) were inflicted with fracture of the Metacarpals, patients were inflicted with fracture of the Tibia are 7 in number i.e. 8.75%, Ulna – 5 in number (6.25%), Fibula – 2 in number (2.5 %), Calcaneum -2 in number (2.5 %), patella 01 in number (1.25%), Scaphoid -1 in number (1.25 %). ribs 04 in number (5 %), Clavicle 03 in numbers (3.75%). So, it is observed that most patients suffered from injuries of the forearm; which are prone to be injured in a trauma, whilst trying to support body against the fall.

Hormone PTH (parathyroid hormone) activity during fracture healing were analyzed and evaluated in both groups, serum analysis was performed as per the standard procedure on 1st day (baseline), 7th, 21st and 31st day. Kits used were DIA source hPTH- ELISA kit Manufactured by –DIA source immunoassay S.A. Rue du bosquet, 2, B-1348 Louvain-la-neuve, Belgium for PTH analysis.

Table 1. Shows effect on Serum hPTH at different time points

Group	Baseline	Day 7	Day 21	Day 31
A	26.78 ±9.06	29.30 ±9.44	51.60± 9.28	34.90± 7.43
B	30.78± 7.51	37.15 ±14.57	32.95± 8.95	29.20 ±7.47

Table 2: Comparison of Mean Serum Parathyroid Hormone at different time point in each group (Repeated measure ANOVA)

			Multiple comparison		
	F-value	**p-value**	**Baseline vs Day 7**	**Baseline vs Day 21**	**Day 21 vs Day31**
Group A	98.89	<0.0001, HS	p>0.05, NS	<0.001, HS	<0.001, HS
Group B	6.693	<0.0001, HS	<0.001, HS	>0.05, NS	>0.05, HS

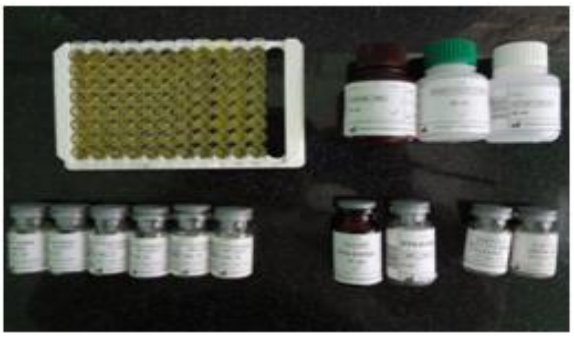
The data obtained during the study were subjected to statistics analysis by repeated measure ANOVA test and wilcoxon Rank sum test it reveals that at different time points mean serum hPTH in Group A (Treated Group) was 26.78 ±9.06, 29.30 ±9.44, 51.60± 9.28 & it was 34.90± 7.43 at baseline, 7th, 21st and 31st Day respectively. Mean Serum

hPTH in Group B (Control Group) was 30.78± 7.51, 37.15 ±14.57, 32.95± 8.95 and 29.20 ±7.47 at baseline, 7th, 21st and 31st Day respectively.

On comparison of Mean Serum Parathyroid Hormone at different time point in each Group by Repeated measure ANOVA test it was observed that In Group A serum PTH was significantly different at different time points (f- = 98.89, P> 0.0001) no significant change in serum PTH was observed at day 7th from baseline (P>0.05) but it was significantly increased on day 21st (p<0.001) and also at day 31st (P<0.001) which is highly significant. In Group B Serum hPTH level was significantly increased at day 7th (p<0.001,HS) but no significant change was noted at day 21st (p>0.05, NS) and day 31st (p>0.05,NS).

Comparison of change in serum parathyroid Hormone at day 7th, 21st and 31st Day from baseline between 2 Groups by wilcoxon Rank sum test shows Mean serum parathyroid Hormone on day 7th in Group A was -2.52± 11.95 and -6.37 ±12.03 in Group B. No significant difference is found between two groups. (p-value is 0.155). While mean change in serum parathyroid Hormone on day 21st from baseline in Group A was -24.82± 9.23 and -2.17± 6.18 in Group B. Sr. PTH was significantly increased in group A as compared to group B (p-value is <0.0001,HS). On day 31st mean change in serum parathyroid Hormone in Group A was -8.12± 9.22 and 1.57± 4.77 in Group B. Sr. PTH was significantly increased in group A as compared to group B (p-value is <0.0001,HS).

Above analysis shows that serum PTH hormone in group A was significantly elevated on 21st and 31st day when compared to baseline and 7th day But shows regular increasing pattern up to day 21st and from day 31st it start to lowering. Such pattern was not found in control group in this group hPTH elevated only on day 7th and further it remains at insignificant level up to day 31st. This shows significant differences in Means of group A than group B. It denotes drug *Ciccus quadrangularis* has property to fluctuate serum PTH and also suggests that it may early initiate and continuously stimulates osteoblastic activity during fracture healing period hence early bone healing and mineralization (callus hardening) may possible. This activity helps to reduce bone maturation period and so reduces the immobilization period and ultimately early rehabilitation can possible.



This hPTH fluctuation is because of only drug *Ciccus Quadrangularis* property and reason for it is that this fluctuation pattern is seen in only group A. This may be due to *Cissus quadrangulari s* causes less amount of tissue reaction in the fractured region leading to optimum decalcification in the early stage with minimum of callus formation. Hence deposition of calcium is just enough to join the two broken segments of bone so that it's remodeling takes much faster in the treated group as compared with controls. *Cissus quadrangularis* may builds up the chemical composition of the fractured bone namely its mucopolysaccharides, collagen, calcium, phosphorus and others as well as its functional efficiency. Early completion of calcification process and earlier remodeling phenomenon may lead to early recovery of patients.

CONCLUSIONS

1. In spite of lack of use of herbal remedies for fracture lot of references regarding drugs which may act on facture healing and its acceleration were available in Ayurvedic texts.
2. *Cissus quadrangularis* is a pharmacological agent for acceleration of bone healing.
3. *Cissus quadrangularis* treated group shows elevation pattern of serum hPTH, early initiation of bone resorption with early initiation of osteoblastic activity and continuous up to bone maturation so hardening of callus at fractured site may also quicker and this may helps to reduction in healing period or immobilization period and so early rehabilitation is possible.
4. Drug *Cissus quadrangularis* accelerates bone fracture healing, can be easily prepared and can be safely administered orally without any serious or adverse effects.

Future Perspectives

1. Assessment with PTH Hormone alone is still debatable. These results can be strengthened by involving other assessment parameters like and biochemical parameters calcium and phosphorus, bone matrix density, Computed tomography and microangiography (to know vascularisation at fractured site).
2. By increasing sample size, number of weekly follow - ups up to 8thweek, and including other assessment parameters, further research work is recommended at higher centre having sufficient attendance of fracture patients so that it may be helpful to draw the accurate conclusion in establishing the useful and an effective approach in the management of Bone fractures.

3. The Accuracy of results may be achieved by conducting Multicentre studies.

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