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Research Article

# EFFECT OF ALENDRONATE ON THE HEALING TIME OF DISTAL RADIAL FRACTURES TREATED CONSERVATIVELY: AN OBSERVATIONAL STUDY

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**ABSTRACT**

**Objective:** Although fragility fractures of the distal radius are common, osteoporosis treatment requires exploration as attempts to improve postfracture investigations have been only partially successful. Bisphosphonates may help minimize the risk of secondary fractures but being a potent antiresorptive agent; it raises concerns about adverse effects on the healing process. This observational study examines the effect of bisphosphonate (alendronate) on healing of acute fractures of distal radius through 66 patients aged >45 years admitted to two tertiary care hospitals in Mangalore from May 2014 to September 2016.

**Methods:** The methodology consists of purposive sampling from two groups: Control having 33 patients not on alendronate therapy and cases comprising 33 who are on alendronate as part of prophylaxis for osteoporosis before fracture occurrence, with outpatient reviews at 2-week intervals starting from the 6$^{th}$ till fracture union seen. At each visit, plain radiographs of the involved wrist were taken to yield time to cortical bridging, with range of active movement of the affected wrist taken using a goniometer. Data were analyzed using Statistical Package for the Social Sciences software version 17.0 for t values, p values and correlations and results were presented in the form of graphs and tables.

**Results:** No significant differences were observed in the groups (as per p values) w.r.t. gender (0.804), age (0.835), time to healing (1.000), dorsiflexion (0.956), palmar flexion (0.670), ulnar deviation (0.441), radial deviation (1.000), supination (0.132), or pronation (0.302). Quick Disabilities of the Arm, Shoulder and Hand score did not differ by >95% between the groups over the analysis period.

**Conclusion:** It was observed that alendronate administration in distal radius fractures did not appear to delay fracture healing times radiologically or clinically.

**Keywords:** Fragility fracture, Osteoporosis, Distal radius, Bisphosphonate, Alendronate.

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## INTRODUCTION

Although fragility fractures of the distal radius are common mostly in women in their 60s or 70s [1], treatment for osteoporosis after such fractures requires in-depth exploration. These fractures are seen to occur at a younger age in patients in comparison with other major osteoporotic fractures [2] and are the most common fractures to occur in the postmenopausal period [3]. Treatments targeted at improving postfracture investigations of osteoporosis have only been partially successful [4].

Treatment using bisphosphonates following a fracture could help in minimizing the risk of a secondary fracture [5]. However, the possibilities of adverse effects of these drugs on the healing process of fractures due to them being antiresorptive agents must always be considered [6]. Tests have been performed on both animals as well as humans in different studies to understand the interaction between bisphosphonates and the fracture healing process. Animal studies have indicated that inhibition of the hard callus remodeling to mature lamella bone occurs as a consequence of bisphosphonates [7,8]. However, studies on humans, in the same manner, have not led to definitive results [9].

The objective of this study is to "examine the effect of bisphosphonate (alendronate) on the healing of acute fractures of the distal radius." The study population consisted of 66 patients aged 45 years and above, who were admitted to the Government Wenlock Hospital and the Kasturba Medical College (KMC) Hospital in Attavar, Mangalore, from May 2014 to September 2016.

The scope of the study extends to determining the level to which administration of alendronate on patients has changed the way that their fractures have healed with reference to those who were not on the alendronate therapy, by examining time of healing, and functional evaluation through Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) scores.

## METHODS

A total of 66 patients aged 45 years and above with acute fragility fractures of the distal radius who presented themselves to the outpatient department of the Government Wenlock Hospital and KMC, Mangalore, from the period dating from May 2014 to September 2016, were considered for this study. 38 patients were excluded from the study based on exclusion criteria and noncompliance with regular follow-up. Group allocation was carried out based on the patients visit to the hospital, with cases and controls alternating with each other. It was found that patients who did not take prophylaxis outweighed patients who did. Hence, once each case was selected, every other patient who satisfied as a control was discarded from the study until a patient who met the criteria for a case was enrolled. 127 patients who met the criteria for control were thereby discarded in the process. The study has been done in compliance with and on approval from the Institutional Ethics Committee, KMC, Mangalore.

Patients with associated fracture of the ulnar styloid were not excluded from the study. Patients with rheumatoid arthritis, chronic renal disease, dementia, open fractures, associated neurovascular complications identified at the time of enrollment, fractures with significant bone loss requiring bone graft or other graft materials, a concomitant fracture of metaphysis of distal ulna and comminuted fractures were excluded from this study.

Fractures were reduced manually under a hematoma block and visualized under image intensifier or using a radiograph. Those fractures which did not achieve reduction were taken up for surgical procedures and therefore excluded from the study. The fracture patterns were classified based on AO system.

Patients were made to complete the QuickDASH questionnaire to evaluate preinjury status. The QuickDASH is a validated 11-item questionnaire for the evaluation of upper extremity symptoms and function. Along with the QuickDASH questionnaire, the patients were required to fill a consent form for enrolment into the study along with details of age, sex, and hospital registration number. Patients were given follow-up dates 6 weeks after the first visit. When a patient arrived for the first follow-up visit at 6 weeks, plain anteroposterior (AP) and lateral view radiographs of the involved wrist were taken after removal of plaster cast after which cortical bridging was assessed at the fracture site. Fractures were deemed healed if at least 3 out of 4 cortices were found to be united. If union was not found in the first follow-up visit, they were asked to be available for review at 2-week intervals till union was noticed. At each visit along with plain radiographs, range of active movements (flexion, extension, supination, pronation, radial, and ulnar deviation) were measured with the assistance of a goniometer.

The following parameters were measured for each examined patient.

i. Time of healing (weeks): Time taken from the day of fracture reduction to the establishment of cortical bridging across the fracture fragments assessed from AP and lateral radiographs (union of 3 out of 4 cortices)
ii. QuickDASH score: Questionnaire which helps to determine preinjury status (detailed in the previous section)
iii. Dorsi flexion: Backward flexion of the hand [10]
iv. Palmar flexion: Bending the hand toward the palmar surface [10]
v. Ulnar deviation: Movement of the hand toward the ulnar side of the forearm [10]
vi. Radial deviation: Movement of the hand toward the radial side of the forearm [10]
vii. Supination: Turning the palm forward (anteriorly) or upward which is performed by lateral rotation of the forearm [10]
viii. Pronation: Turning the palm backward (posteriorly) which is performed by medial rotation of the forearm [10].

## RESULTS

The primary outcome was the process of healing assessed radiologically by the observer. Other parameters were the range of movements of the wrist joint and the functional restriction as assessed by QuickDASH.

The following statistics were used for each of the above parameters to understand the statistical significance of each of them: Mean, standard deviation, t- and p-values as well as the Pearson's correlation coefficient. From Table 1, it can be inferred that all parameters are seen to have a statistical significance which is <95% when looking at the cases and controls groups which are below the required range as per this study.

These results show that there is not a significant difference between patients who were being administered alendronate, to those who were not on the treatment, as demonstrated by their high p>0.05.

Graphs 1 and 2 shows the arithmetic mean of both the groups as well as for the total set for QuickDASH score as well as for the time of healing (weeks).

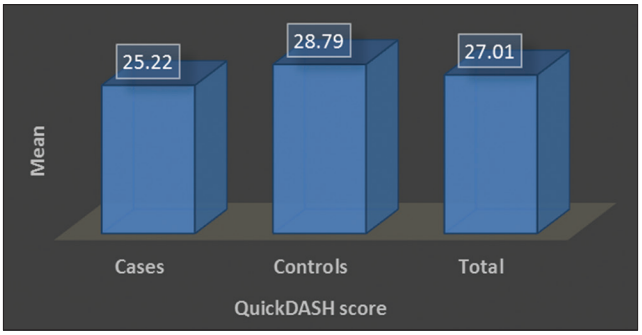
When looking at the correlations between parameters, the following results were seen as shown in Tables 2 and 3, which have been obtained from the software.

On close examination of the correlation values presented above, it can be seen that QuickDASH score correlates negatively with all other parameters in both cases and controls groupings. Time of healing correlates positively with all wrist movements and negatively with

**Table 1: Statistical derivations for cases, controls, and total groupings**

| Parameter | Group | N | Mean±SD | t-value | p value |
|---|---|---|---|---|---|
| Gender | Cases | 33 | - | 0.062 | 0.804 |
| | Controls | 33 | | | |
| | Total | 66 | | | |
| Age | Cases | 33 | 63.70±10.054 | 0.210 | 0.835 NS |
| | Controls | 33 | 64.24±11.068 | | |
| | Total | 66 | 63.97±10.495 | | |
| QuickDASH score | Cases | 33 | 25.22±7.639 | 1.809 | 0.075 NS |
| | Controls | 33 | 28.79±8.367 | | |
| | Total | 66 | 27.01±8.150 | | |
| Time of healing (weeks) | Cases | 33 | 7.27±1.790 | 0.000 | 1.000 NS |
| | Controls | 33 | 7.27±1.989 | | |
| | Total | 66 | 7.27±1.877 | | |
| Dorsi flexion | Cases | 33 | 49.09±11.555 | 0.055 | 0.956 NS |
| | Controls | 33 | 48.94±10.662 | | |
| | Total | 66 | 49.02±11.032 | | |
| Palmar flexion | Cases | 33 | 60.00±12.374 | 0.428 | 0.670 NS |
| | Controls | 33 | 58.79±10.535 | | |
| | Total | 66 | 59.39±11.419 | | |
| Ulnar deviation | Cases | 33 | 20.61±6.344 | 0.776 | 0.441 NS |
| | Controls | 33 | 19.39±6.344 | | |
| | Total | 66 | 20.00±6.325 | | |
| Radial deviation | Cases | 33 | 12.27±5.741 | 0.000 | 1.000 NS |
| | Controls | 33 | 12.27±5.168 | | |
| | Total | 66 | 12.27±5.419 | | |
| Supination | Cases | 33 | 58.64±12.328 | 1.525 | 0.132 NS |
| | Controls | 33 | 54.09±11.888 | | |
| | Total | 66 | 56.36±12.233 | | |
| Pronation | Cases | 33 | 45.61±12.976 | 1.040 | 0.302 NS |
| | Controls | 33 | 42.47±13.056 | | |
| | Total | 66 | 43.94±13.024 | | |

DASH: Disabilities of the Arm, Shoulder and Hand




**Graph 1: Mean of groups and total for Quick Disabilities of the Arm, Shoulder and Hand score**

QuickDASH score in cases group, whereas in controls, it varies with each parameter. Correlations with significance >99% have been highlighted with ** and those with >95% significance with * as shown in Tables 1-3.

## DISCUSSION

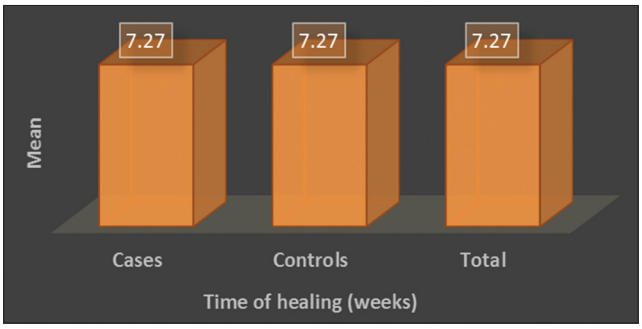
The study that was done in this paper aimed at examining the effect of alendronate on the healing of acute distal radius fractures in 66 patients aged higher than 45. It was concluded from this observational study that the administration of alendronate did not cause any adverse effects, as noted from radiological and clinical findings. There were found to be no significant differences in time of healing, QuickDASH score or any of the active wrist movements between patients who had been administered alendronate in comparison with those who were not on it when looking at statistical significances.

Bisphosphonates are effective therapeutic agents for an array of diseases related to the bone as they are good inhibitors of bone

**Table 2: Correlations between parameters for cases group**

| Parameters | QuickDASH score | Time of healing (weeks) | Dorsi flexion (0-70) | Palmar flexion (0-80) | Ulnar deviation (0-35) | Radial deviation (0-25) | Supination (0-80) | Pronation (0-70) |
|---|---|---|---|---|---|---|---|---|
| QuickDASH score | | | | | | | | |
| Pearson correlation | | −0.095 | −0.895** | −0.845** | −0.798** | −0.773** | −0.847** | −0.877** |
| p | | 0.598 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| N | | 33 | 33 | 33 | 33 | 33 | 33 | 33 |
| Time of healing (weeks) | | | | | | | | |
| Pearson correlation | | | 0.118 | 0.000 | 0.123 | 0.379* | 0.109 | 0.154 |
| p | | | 0.513 | 1.000 | 0.497 | 0.030 | 0.544 | 0.392 |
| N | | | 33 | 33 | 33 | 33 | 33 | 33 |
| Dorsi flexion (0-70) | | | | | | | | |
| Pearson correlation | ** | | | 0.907** | 0.754** | 0.692** | 0.836** | 0.837** |
| p | | | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| N | | | | 33 | 33 | 33 | 33 | 33 |
| Palmar flexion (0-80) | | | | | | | | |
| Pearson correlation | ** | | ** | | 0.637** | 0.594** | 0.773** | 0.744** |
| p | | | | | 0.000 | 0.00 | 0.000 | 0.000 |
| N | | | | | 33 | 33 | 33 | 33 |
| Ulnar deviation (0-35) | | | | | | | | |
| Pearson correlation | ** | | ** | ** | | 0.776** | 0.760** | 0.812** |
| p | | | | | | 0.000 | 0.000 | 0.000 |
| N | | | | | | 33 | 33 | 33 |
| Radial deviation (0-25) | | | | | | | | |
| Pearson correlation | ** | * | ** | ** | ** | | 0.707** | 0.809** |
| p | | | | | | | 0.000 | 0.000 |
| N | | | | | | | 33 | 33 |
| Supination (0-80) | | | | | | | | |
| Pearson correlation | ** | | ** | ** | ** | ** | | 0.928** |
| p | | | | | | | | 0.000 |
| N | | | | | | | | 33 |
| Pronation (0-70) | | | | | | | | |
| Pearson correlation | ** | | ** | ** | ** | ** | ** | |

**Correlation is significant at the 0.01 level (two-tailed test). *Correlation is significant at the 0.05 level (two-tailed test). QuickDASH: Quick Disabilities of the Arm, Shoulder and Hand




**Graph 2: Mean of groups and total for time of healing (weeks)**

resorption [7]. Due to their effectiveness in reducing the incidence of fragility structures, they are highly favored as therapeutic agents for osteoporosis [7]. They are categorized into nitrogen-containing and non-nitrogen-containing bisphosphonates based on their mechanism of action. Nitrogen-containing bisphosphonates have the property of persisting for a considerable amount of time on the surface of the bone. This has, in turn, resulted in an increased use of these agents in clinical practice through dosing intermittently [7]. Alendronate is a bisphosphonate which contains nitrogen which is administered orally and the above-stated reasons have led to it being given at a daily and weekly dosage of almost 7 times that of the standard daily dose [7]. It is estimated to have 10 years as its skeletal half-life, and thus, it is crucial to dissect the possible consequences of intake of this drug because of its intrinsic ability to suppress osteoclast function which affects the process of fracture repair [11]. This could result in patients not achieving full recovery of this function for quite a period. However, due to it being a low-cost bisphosphonate with a wide spectrum of fracture efficacy, it is considered in most of the cases as the first line of treatment [12].

Tripathy *et al*. [13] in their study determine the clinical profile and prescription pattern of drugs in the treatment of osteoporosis in a tertiary care center in Karnataka noted in their findings that alendronate was the most commonly prescribed bisphosphonate (55.56%), prescribed as once weekly or once daily dose. Alendronate acts as a potent antiresorptive agent and inhibits farnesyl pyrophosphate synthase in osteoclasts, which need prenylated proteins for their function and survival [9]. As described in the paper by Uchiyama *et al*. [9] in 2013, the process of fracture healing is in the following order, though there exists some overlap between the stages: Inflammation, soft callus formation, hard callus formation, and hard callus remodeling. In the hard callus remodeling stage, osteoclasts are very much active. Alendronate is not seen to affect directly osteoblasts or other cells which participate in any of the first three stages mentioned above. Therefore, it can be inferred that callus formation radiologically, may not be affected by alendronate in a substantial manner; however, delays in remodeling of the hard callus could occur, as are also indicated in various animal studies. The process of bone remodeling goes hand in hand with other processes such as cartilage mineralization, vascular invasion as well as formation of the woven bone. Furthermore, osteoclasts are seen to be active from the beginning stages of fracture healing, removing necrotic bone from the fracture site. Hence, there always exists a possibility of delay in fracture healing occurring as a result of osteoclast dysfunction when administration of alendronate is started immediately.

Uchiyama *et al*., in 2013, [9] concluded from their study that administration of alendronate, early on after an operatively treated distal radius fracture did not seem to delay the healing of the fracture either radiologically or clinically, from their analysis of 80 patients overall with

**Table 3: Correlations between parameters for controls group**

| Parameters | QuickDASH score | Time of healing (weeks) | Dorsi flexion (0-70) | Palmar flexion (0-80) | Ulnar deviation (0-35) | Radial deviation (0-25) | Supination (0-80) | Pronation (0-70) |
|---|---|---|---|---|---|---|---|---|
| QuickDASH score | | | | | | | | |
| Pearson correlation | | −0.031 | −0.735** | −0.645** | −0.586** | −0.733** | −0.715** | −0.726** |
| p | | 0.864 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| N | | 33 | 33 | 33 | 33 | 33 | 33 | 33 |
| Time of healing (weeks) | | | | | | | | |
| Pearson correlation | | | 0.021 | −0.014 | 0.137 | 0.014 | −0.135 | −0.151 |
| p | | | 0.906 | 0.940 | 0.446 | 0.939 | 0.455 | 0.402 |
| N | | | 33 | 33 | 33 | 33 | 33 | 33 |
| Dorsi flexion (0-70) | | | | | | | | |
| Pearson correlation | ** | | | 0.872** | 0.579** | 0.598** | 0.744** | 0.832** |
| p | | | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| N | | | | 33 | 33 | 33 | 33 | 33 |
| Palmar flexion (0-80) | | | | | | | | |
| Pearson correlation | ** | | ** | | 0.573** | 0.612** | 0.827** | 0.861** |
| p | | | | | 0.000 | 0.00 | 0.000 | 0.000 |
| N | | | | | 33 | 33 | 33 | 33 |
| Ulnar deviation (0-35) | | | | | | | | |
| Pearson correlation | ** | | ** | ** | | 0.734** | 0.593** | 0.630** |
| p | | | | | | 0.000 | 0.000 | 0.000 |
| N | | | | | | 33 | 33 | 33 |
| Radial deviation (0-25) | | | | | | | | |
| Pearson correlation | ** | | ** | ** | ** | | 0.594** | 0.674** |
| p | | | | | | | 0.000 | 0.000 |
| N | | | | | | | 33 | 33 |
| Supination (0-80) | | | | | | | | |
| Pearson correlation | ** | | ** | ** | ** | ** | | 0.895** |
| p | | | | | | | | 0.000 |
| N | | | | | | | | 33 |
| Pronation (0-70) | | | | | | | | |
| Pearson correlation | ** | | ** | ** | ** | ** | ** | |

**Correlation is significant at the 0.01 level (two-tailed test). QuickDASH: Quick Disabilities of the Arm, Shoulder and Hand

40 being administered alendronate and 40, not being administered the drug. A double-blind study, in 2000, conducted by Van Der Poest Clement *et al*. [14] to examine how bone loss after a fracture in women having Colles' fracture and postmenopausal osteoporosis is affected by alendronate; a 10 mg dosage of the drug or placebo was administered to 37 women who were diagnosed with distal forearm fracture and low bone mineral density (BMD) of the lumbar spine. Heightened levels of resorption combined with decreased formation resulted in bone loss after a fracture occurrence and in the immobilization period. Hike in the BMD of the hip and lumbar spine, as well as decrease in nonspine fracture incidence in postmenopausal women with osteoporosis, was seen to occur as a result of alendronate. A study conducted by Rozental *et al*. [15], in 2009, looked into a comparison of healing rates of distal radius fractures in patients who were on bisphosphonate therapy at the injury time with those who were not on it. A total of 196 patients were considered out of which the patients who were on the therapy were 43 and those who were not, made up the control group with 153 patients. The factors which affected time to radiographic union were assessed using regression analysis and it was discovered that the average time to union was a bit lengthier in patients who were on bisphosphonate as opposed to those who were not it, with a ratio of 55 to 49 days. Thus, an increased time of healing was noted with bisphosphonate use, but that was deemed not satisfactory enough to demonstrate a clinical significance. Gong *et al*. [16] conducted a study in 2012 to determine the effect of early administration of bisphosphonate on the healing of osteoporotic distal radius fractures. This study focused on a randomized clinical trial to determine how safe it is for a patient who has an acute distal radius fracture to be administered bisphosphonates. It was inferred that osteoporotic medication after stable fracture fixation can be started early on in patients who faced a possible risk of future fracture. In their study to evaluate the effectiveness of certain bisphosphonates for the treatment of osteoporosis in postmenopausal women over the age of 50 in Tirana, Miraçi *et al.* [17] considered both alendronate as well as ibandronate.

Although the beneficial reasons for bisphosphonates may be justified from the improvements seen in patients, it is necessary to put in a word about the possible consequences of their usage. Bisphosphonates suppress the process of bone resorption by inhibiting osteoclast formation, which could in turn cause changes in remodeling, bone mineral content as well as affect the tensile strength of the healing bone [18]. In addition, a preferential deposition of oral and intravenous bisphosphonates at the site of an acute fracture has been noticed in many cases, and this could significantly affect clinical healing of these fractures [18]. Case studies performed by Odvina *et al*. [6], Goh *et al*. [19], and Kwek *et al*. [20] which looked into sets of atypical nonspine fractures of patients who have been on bisphosphonate therapy for a long period of time raised concerns about its usage. It was observed that fracture healing was delayed or absent for 3 months up to 2 years for a significant number of these patients while they were on therapy. Atypical femoral fractures and osteonecrosis of the jaw are some of the consequences of the use of bisphosphonates on a long duration basis, and thus, the exact duration of administration has been a topic of dispute in the field of orthopedics [12]. It was seen that inhibition of the hard callus remodeling to mature lamella bone occurs as a result of bisphosphonate use in several animal studies which have been conducted [7,8]. While the risk of using bisphosphonates has been found to be statistically significant in many of these studies, it is a worthy point that the clinical significance is still unclear. Bisphosphonates are seen to be highly beneficial in decreasing fracture risk and it is a fact that the anguish and fatality associated with a new fracture occurrence is higher than that of nonunions which have been seen [15]. Hence, a proper evaluation of when to start the treatment following a fracture requires in-depth analysis as a delayed start must not result in initiation issues with these agents.

There are several limitations to this study which include the following points: Difficulty in finding out whether the patient has shown compliance in administration of the drug, limited number of subjects resulting in data compilation which may not be exactly accurate in a

real situation and inter observer variability in assessment of fracture healing.

## CONCLUSION

It was observed that alendronate administration in distal radius fractures did not seem to delay fracture healing times either radiologically or clinically.

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