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Original Research Article

Comprehensive Study of Role of Zolendronate in Combination with Calcium in Fracture Disease Management

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Abstract: Fracture Disease is rare avascular necrosis following the immobilization of fractures occurs often in older and inactive age groups secondary to sympathetic over activity around the immobilized parts. No standard of treatment still exists for treating early stages of AVN, of the cases eventually progressing to a late arthritic stage needing surgical intervention. Bisphosphonates have been shown to prevent disease progression, bone collapse, and the requirement for surgery in avascular necrosis of bone following immobilization of fracture commonly around wrist and hand. The present study is conducted to evaluate the response of bisphosphonates in the l management of the early stages of AVN following fracture disease which usually is untreated where pt presents with stiffness and swelling around the hand and finger and foot. ***Materials and methods*:** Prospectively collected data of 80 patients diagnosed with an fracture disease and treated with the combination of intravenous zolendronic acid (ZA) with calcium supplementation for 2-3 consecutive years year, between Jan 2016 to Dec 2018, was evaluated retrospectively. Clinical evaluation was done using the visual analogue scale (VAS), mean analgesic requirement, and range of motion. Radiographs were taken to monitor radiological collapse, and evaluate radiological progression and bone marrow and cortical changes at regular intervals of 6 moths each, changes were categorized based on clinical evolution of progress in osteosynthesis based on regular wt bearing and active mobilization of the affected part. ***Results:*** In our analysis of 80 patients (9 lost to follow-up), 55 patients had fracture disease around the wrist and 53 patients were treated by osteopaths and 2 by casts, and 25 patients had fracture disease around the foot and metatarsal head were treated by osteopaths. Pain relief with the drop in VAS score was seen at a mean duration of 6-8 weeks (range 5–15 weeks) after the start of therapy. ZOLendronate maintained the mean level of total ALP at the middle of the reference range, showed linear increase in total ALP from the 6-month post-treatment time-point a 50% reduction in mean analgesic requirement was achieved in the first 3 weeks (2-11 weeks). Radiological improvement in 33 patients at 6 months and in 70 patients (85.4%) at 1 year. Only 1 out of 71 patients enrolled required sympathectomy around the brachial plexus. ***Conclusion:*** A combination of oral calcium and intravenous zolendronic acid provides a pragmatic solution to this rare entity of Fracture Disease, where no standard treatment exists.

Keywords: Bisphosphonates, Fracture Disease, Avascular necrosis, VAS score, Bone marrow edema, sympathectomy, Osteopaths.

INTRODUCTION

Fracture disease, which is a complication of fracture treatment and immobilization, is defined as atrophy of bone, soft tissues, nail, skin, and cartilage. Reflex sympathetic dystrophy may sometimes occur and further complicate the fracture. This constellation of symptoms and physical changes has been called "Fracture disease." Like proud flesh and suppuration in soft tissue healing, it is not a necessary part of fracture repair and can be avoided, Prolonged immobilization, especially in a nonfunctional cast treatment by osteopaths with tight bandages with prolonged application, can lead to a vicious cycle of pain, swelling, and unresolved edema. Edema fluid is a

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proteinaceous exudate that will congeal into scar tissue around joints and tendons and cause joint stiffness, contracture, and tendon adhesions. Muscle atrophy, brawny skin /induration, and diffuse osteoporosis followed by stiffness AND skin atrophy with muscle wasting follows. It was commonly diagnosed in the recovery period after distal radius fracture.

Although arthrodesis gives good pain relief, it leads to a significant restriction of activities especially in the Asian population, is the final resort.

As stated by George Perkins most disability occurs following treatment of fracture rather than the actual pathology.

A single 5-mg infusion of zoledronic acid restores biochemical markers of bone turnover, by greater binding affinity to hydroxyapatite and increased potency in terms of inhibition of osteoclastic bone resorption.

ZOLendronate binds strongly to hydroxyapatite so that it is more likely to be retained in bone during the remodeling cycle because of reattachment of bisphosphonate released during resorption. The potency of the drug in inhibiting osteoclastic bone resorption through an action on the key enzyme farnesyl diphosphate synthase, administration effectively prevented BMD loss and increased BMD.

Zoledronic acid has the potential to improve clinical outcomes by reducing the osteoclastic activity fracture disease patients. Zoledronic acid is an aminobisphosphonate with a high affinity for mineralized bone. Administered as an intravenous infusion over at least 15 min, it rapidly localizes to bone, where it inhibits osteoclastic bone resorption by inhibiting the action of the enzyme farnesyl pyrophosphate synthase in the mevalonate pathway. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity for bone mineral.

Staging of the disease was done as per the VAS based on the symptoms and clinical findings.

Satge1: Skin changes with redness and minimal restriction of movements in the minor joints.

Stage 2: Diffuse skin atrophy with moderate restriction of movements in major joints with radiological gross osteopenia with BMD z score-3.5

Stage 3: Muscle atrophy, brawny skin /induration, and diffuse osteoporosis followed by stiffness with muscle wasting

MATERIALS AND METHODS

Prospectively collected data of 80 patients diagnosed with an fracture disease and treated with the combination of intravenous zolendronic acid (ZA) (inj Rockfos 5mg) with calcium supplementation for 2-3 consecutive years year, between Jan 2016 to Dec 2018, was evaluated retrospectively.

Clinical evaluation was done using the visual analogue scale (VAS), mean analgesic requirement, and range of motion. Radiographs were taken to monitor radiological collapse, and evaluate radiological progression and bone marrow and cortical changes at regular intervals of 6 mths each, changes were categorized based on clinical evolution of progress in osteosynthesis based on regular wt bearing and active mobilization of the affected part.

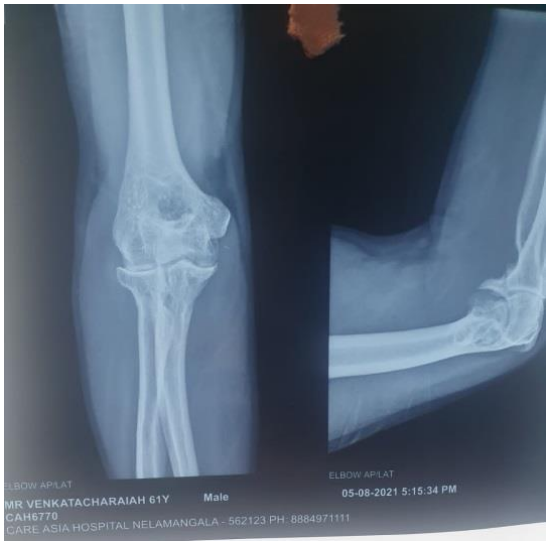
RESULTS

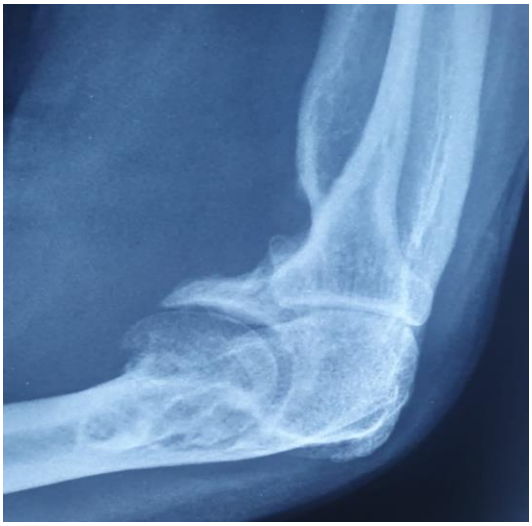
In our analysis of 80 patients (9 lost to follow-up), 55 patients had fracture disease around the wrist and 53 patients were treated by osteopaths and 2 by casts, and 25 patients had fracture disease around the foot and metatarsal head were treated by osteopaths.

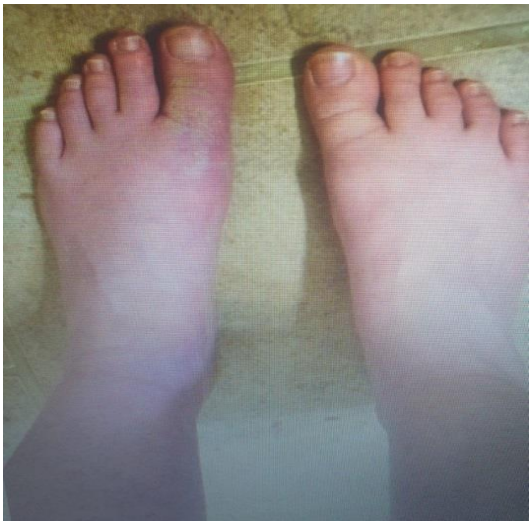
Pain relief with the drop in VAS score was seen at a mean duration of 6-8 weeks (range 5–15 weeks) after the start of therapy.

ZOLendronate maintained the mean level of total ALP at the middle of the reference range, showed linear increase in total ALP from the 6-month post-treatment time-point.

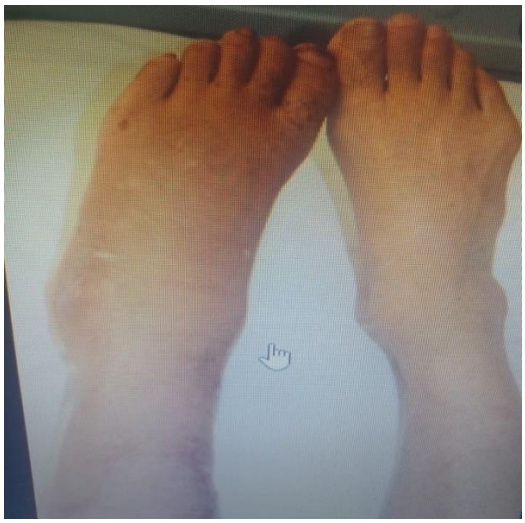
A 50% reduction in mean analgesic requirement was achieved in the first 3 weeks (2-11 weeks). Radiological improvement in 33 patients at 6 months and in 70 patients (85.4%) at 1 year. Only 1 out of 71 patients enrolled required sympathectomy around the br



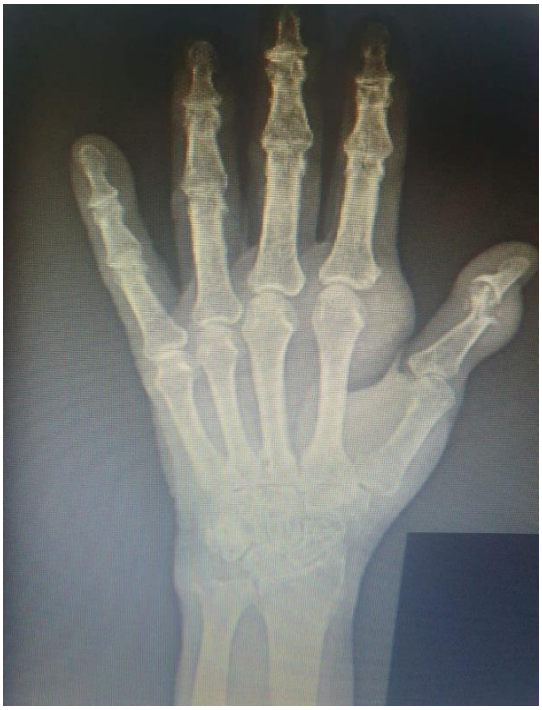




Skin pale cynotic and muscle atrophy with loss skin creases with loss of skin and hair



Disuse skin atrophy with brittle nails and shiny creases



X-ray shows radiolucent lines with osteopenia changes following loose immobilization of colles fractures

Post treatment improvements in Range of movement, skin creases reappear with hair growth

Table-1: Table showing the demographic details of the patient enrolled in the study

S. No.	Age/sex	BMI	Side of affection	Dominant (D)/non-dominant (ND)	Site of affection	Stage at start of therapy	Last follow-up (months)	Stage at final follow-up
1	64/M	28.8	Right	D	wrist	2	45	1
2	50/F	26.5	Left	ND	wrist	1	48	2
3	18/M	20.8	Right	D	wrist	2	25	3
4	28/M	21.6	Left	ND	wrist	2	25	2
5	30/M	19.6	Left	ND	wrist	2	14	3
6	47/M	32.4	Right	-	wrist	2	52	2
7	65/F	26.7	Right	-	wrist	2	44	3
8	66/M	35.6	Right	-	wrist	1	56	3
9	50/M	33.2	Left	-	wrist	2	50	2
10	23/M	21.4	Right	D	wrist	2	32	2
11	32/M	31.9	Left	ND	wrist	2	25	2
12	52/F	20.6	Left	ND	wrist	2	26	2
13	30/M	16.8	Right	D	wrist	2	14	3
14	23/F	21.3	Right	D	wrist	1	48	2
15	25/F	23.6	Right	-	wrist	1	46	2
16	42/M	19.4	Right	-	wrist	1	24	1
17	27/F	28.8	Left	-	wrist	1	36	2
19	64/M	28.8	Right	D	Foot and ankle	2	45	1
20	50/F	26.5	Left	ND	Foot and ankle	1	48	2
21	18/M	20.8	Right	D	Foot and ankle	2	25	3
22	28/M	21.6	Left	ND	Foot and ankle	2	25	2
23	30/M	19.6	Left	ND	Foot and ankle	2	14	3
24	47/M	32.4	Right	-	Foot and ankle	2	52	2
25	65/F	26.7	Right	-	Foot and ankle	2	44	3
26	66/M	35.6	Right	-	Foot and ankle	1	56	3
27	50/M	33.2	Left	-	Foot and ankle	2	50	2
28	23/M	21.4	Right	D	Foot and ankle	2	32	2
29	32/M	31.9	Left	ND	Foot and ankle	2	25	2
30	52/F	20.6	Left	ND	Foot and ankle	2	26	2
31	30/M	16.8	Right	D	Foot and ankle	2	14	3
32	23/F	21.3	Right	D	Foot and ankle	1	48	2
33	25/F	23.6	Right	-	Foot and ankle	1	46	2
34	42/M	19.4	Right	-	Foot and ankle	1	24	1
35	27/F	28.8	Left	-	Foot and ankle	1	36	2
36	32/M	31.2	Right	-	Metatarsal head	1	26	1
37	30/M	19.6	Left	ND	Foot and ankle	2	14	3
385	47/M	32.4	Right	-	Foot and ankle	2	52	2
39	65/F	26.7	Right	-	Foot and ankle	2	44	3
40	50/M	33.2	Left	-	Foot and ankle	2	50	2

Assessment

At presentation and subsequent follow-ups, patients were assessed clinically for pain, range of movement, and mean analgesic requirement. Visual analogue scale (VAS) was used to assess the intensity of pain and was recorded on a verbal response scale of 0–10 (0 for no pain, 10 for the most severe). Radiological assessment was done with plain radiographs in anteroposterior and lateral views. Diffuses osteoporosis was passed along with the BMD for the radius, scaphoid, lunate, and metacarpals metatarsal head was classified as per Cruess modified Ficat and Artlet Herbert and Lanzetta classification, respectively.

All patients were followed up at 6 weeks, 3 months, every 6 months in the first 2 years, and annually thereafter. At each visit, range of movement and intensity of pain (VAS score) along with mean analgesic requirement were recorded. Radiographs and BMD were taken to note down the radiological improvement in terms of resolution of bone marrow edema and to classify the radiological progression or stabilization of the pathology. Clinical failure was considered when pain and disability warranted surgical

intervention. Radiological failure was defined as a progression to arthritis or collapse stage.

Table-2: VAS (visual analogue scale) pain score at all follow up visits

Mean VAS	Baseline	4 weeks	1 year	2 year	Last follow-up
Mean (range)	7.72 (5–9)	3.12 (1–6)	2.44 (0–4)	0.83 (0–3)	0.56 (0–3)
P value (*t* test)		< 0.0001	< 0.0001	< 0.001	< 0.001

DISCUSSION

Out of the 80 patients enrolled in our study, radiological progression to arthritis was seen in only 2 patients at a mean follow-up of 34.3 months (range 14-56 months), while only 1 patient underwent surgery.

Thus, this combination of yearly intravenous zolendronic acid and oral calcium provides a pragmatic solution in the management of fracture disease. It not only provides pain relief but also prevents long-term radiological progression, thus obviating the need for surgery. 94.4 % of our patients in early stages of FD showed good clinical improvement. This combination is well tolerated. Thus, we present a new paradigm in the management of a condition lacking standard management guidelines.

CONCLUSION

A combination of oral calcium and intravenous zolendronic acid provides a pragmatic solution to this rare entity of Fracture Disease, where no standard treatment exists.

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