

# International Journal of Orthopaedics Sciences

E-ISSN: 2395-1958  
P-ISSN: 2706-6630  
IJOS 2020; 6(3): 279-282  
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[www.orthopaper.com](http://www.orthopaper.com)  
Received: 18-05-2020  
Accepted: 22-06-2020

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## A placebo control trial to assess the role of calcitonin in early fracture healing in intertrochanteric fracture treated surgically: A prospective study

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**DOI:** <https://doi.org/10.22271/ortho.2020.v6.i3e.2211>

### Abstract

**Background:** Intertrochanteric fractures often result from trivial injury in the old age patient and is a fracture occurring outside the joint capsule. Calcitonin has been used to treat patients with hip fracture because it is a potent inhibitor of bone resorption. However, its role in decreasing pain intensity, promoting early mobilization and fracture healing is still under debate.

**Method:** We conducted a placebo controlled prospective study over two years from 2018 to 2019 to assess the role of salmon calcitonin administered intranasally, in terms of analgesia and early fracture healing in 40 patients randomised into two groups. Group 1 given intramuscular calcitonin for 7 days followed by intranasal till 10 weeks while group 2 received placebo (Normal saline). Patients were followed up till 10 weeks post-operatively. The mean age was 50.5 years (range 32 years to 68 years) with 28 (70%) female and 12 (30%) male patients and the commonest cause of injury was fall from standing position (80%).

**Results:** There was statistically significant difference between the minimum Rush score in Interventional group vs control group at 6th week and 10<sup>th</sup> week (23 vs 18; 29 vs 23) and maximum score (26 vs 21; 30 vs 28). Similarly, intensity of the pain at 1<sup>st</sup>, 6th and 10th week using WILCOXEN TEST was significantly reduced (p value <0.0001) in test group and control group (p value <0.0001). Similarly, inter-group comparison of intensity of pain as calculated by VAS score at 1st, 6th & 10th week using MANN-WHITNEY test showed that the interventional group had a lesser intensity of pain as compared to the control group (p value <0.0001) helping in early mobilization of the patients.

**Conclusion:** Rate of fracture healing was faster showing early fracture union, complete consolidation of fracture, early disappearance of fracture line and reduced intensity of pain in calcitonin treated group. Hence, therapy of combined intramuscular and intranasal salmon calcitonin given post operatively is useful for early healing and repair of intertrochanteric fractures and offers immediate and lasting pain relief.

**Keywords:** Intertrochanteric fracture, fracture healing, RUSH score, calcitonin

### Introduction

The burden of Intertrochanteric fracture of 250,000 annually and has an increasing morbidity in old age population in the USA. Most of these happen in patients over 6th decade of life, and are more common in females than males (3:1). They often result from trivial injury<sup>[1]</sup>. It occurs outside joint capsule, between lesser and greater trochanters containing thick trabecular bone<sup>[2]</sup>. These fractures account for the largest morbidity in the older population and are usually linked with osteoporosis. They are a result of road traffic accidents in young people (<40 years). Trivial falls from a 5 feet height account for 80% of hip joint fractures in geriatric group and is the common fractures in women above age of 65years<sup>[3]</sup>.

Hip fractures resulting from osteoporosis are increasing socioeconomic problem and cause reduced life quality<sup>[4]</sup>. In females above 5<sup>th</sup> decade of life, on an average lifetime risk of fragility fractures is 40–50 percent and is about two-third lesser in males<sup>[5]</sup>. On an average, it accounted for nine million fracture across the world in the year 2000 leading to loss of five point eight million DAL (disability adjusted life years)<sup>[6]</sup>. Currently, 280,000 fractures occur yearly, with almost half of them due to intertrochanteric fractures. By 2040, the pelvic fracture is expected to rise to 500,000.

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The stability depends on the number of fracture fragments, making such fractures inherently unstable [2]. They have the high post-operative mortality rate and lead to prolonged hospital stay and late mobilization due to the population they commonly affect and lead to poor recovery of functional independence after conventional fracture care [3].

Calcitonin is used to treat patients with hip fracture because it is a potent inhibitor of bone resorption. Age is the most important risk factor for osteoporosis. Calcium loss continues in geriatric age at rate of 1–3% per year and is increased by immobilization. It may be further increased after hip fracture. Calcitonin decreases pain intensity and promote early mobilization, apart from stabilizing ‘callus’ formation and promoting fracture healing [3].

### Method and Patients

40 consecutive patients from age 30-90 years with intertrochanteric fracture diagnosed clinically and radiologically from January 2018 to December 2018 were enrolled in the study after obtaining written informed consent. The sample size was decided based on the annual average of intertrochanteric fractures operated in our hospital over the past 3 years. Patients with Chronic Illness, Metabolic bone diseases, Septic arthritis of hip, Osteomyelitis, Marfans disease, Ehlers Danlos syndrome, and those allergic to calcitonin upon sensitivity testing were excluded. They were subjected to block randomization technique using the Sequentially Numbered, Opaque, Sealed Envelopes (SNOSE). After the surgical treatment, each subject received salmon calcitonin which was administered through intramuscular injection 100 IU OD till POD-7. After POD-7 the patients are administered intranasally for 10 weeks. Calcitonin for 10 weeks or a placebo (normal Saline) for the same duration were administered.

Plain radiography of femur full length in anteroposterior (AP) and lateral views were taken at 1st week, 6th week and 10th week of post-operative period and compared to the other group using Radiographic Union Scale for Hip (RUSH) score. Patients were also assessed for pain at the same time with Visual Analogue Score (VAS). The outcome measure was analysed using SPSS.

### Results

The variables RUSH Scores and VAS scores are discrete in nature, with Median Score an appropriate average for such variables. For discrete variables nonparametric tests are applied which are also based on median. Within the interventional group, the same patient RUSH score was compared using 1-week score as baseline and there was significant improvement in the RUSH score over period of 6 weeks and 10 weeks (p value <0.0001) showing statistical significance, proving that there was fracture healing. Even in the control group the p value <0.0001 shows that the value was statically significant denoting that there was fracture healing even in control group (TABLE 1).

To compare the rate of fracture healing between the interventional group and the control group on basis of RUSH score, MANN-WHITNEY TEST was used. The minimum Rush score in interventional group at 1st week was 14 whereas in control group was 12 and maximum score in interventional group was 16 and control group was 14. The minimum Rush score in interventional group at 6th week was 23 whereas in control group was 18 and maximum score in interventional group was 26 and control group was 21. The minimum Rush score in interventional group at 10th week was 30 whereas in control group was 23 and maximum score in interventional group was 30 and control group was 28. This test signifies that the rate of fracture healing assessed using RUSH score at 1st, 6th and 10th in interventional group was significantly more when compared to control group as p value was <0.0001 (TABLE 2).

When the intensity of pain at 1st week was compared with that at 6th week and 10th week in both the groups independently (WILCOXEN TEST), it had significantly reduced (p value <0.0001). However, those in the control group were not completely pain free (TABLE 3). The intensity of pain as calculated by VAS score was compared between the interventional group and the control group on 1st week, 6th week & 10th week using MANN-WHITNEY test which showed that the interventional group had a lesser intensity of pain as compared to the control group (p value < 0.0001). This helped in early mobilization of the patients (TABLE 4).

**Table 1:** Intra Group Fracture Healing Comparison Using Wilcoxon Test in Test and Control Group (Rush Score)

	Test group			Control group		
	1 week	6 Week	10 Week	1 Week	6 Week	10 Week
Median	15	25	30	12	19	25
Minimum	14	23	29	12	18	23
Maximum	16	26	30	14	21	28
P value	-	< 0.0001	< 0.0001	-	< 0.0001	< 0.0001
Inference	-	HS	HS	-	HS	HS

HS: Highly Significant

**Table 2:** Inter group comparison between rush score done using mann-whitney test

Median for Rush Score								
	Test group	Minimum	Maximum	Control group	Minimum	Maximum	P value	Inference
1 WEEK	15	14	16	12	12	14	< 0.0001	HS
6 WEEK	25	23	26	19	18	21	< 0.0001	HS
10 WEEK	30	29	30	25	23	28	< 0.0001	HS

HS: Highly Significant

**Table 3:** Intra group pain comparison using wilcoxon test in test and control group (vas score)

	Test group			Control group		
	1 week	6 Week	10 Week	1 Week	6 Week	10 Week
Median	4	1	0	5.5	4	1
Minimum	2	1	0	4	3	0

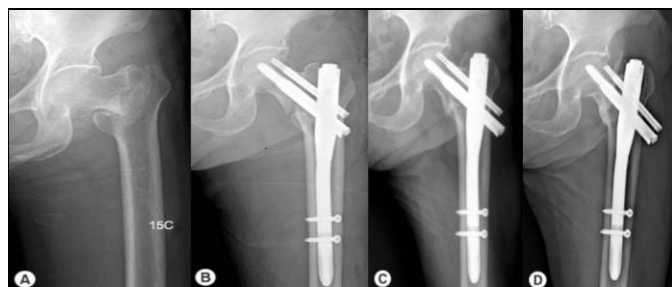
Maximum	4	3	1	7	5	1
P value	-	< 0.0001	< 0.0001	-	< 0.0001	< 0.0001
Inference	-	HS	HS	-	HS	HS

HS: Highly Significant

**Table 4:** Inter group pain comparison between vas score using Mann-Whitney test

Median for vas score								
	Test group	Minimum	Maximum	Control group	Minimum	Maximum	P value	Inference
1 week	4	2	4	5.5	4	7	< 0.0001	HS
6 week	1	1	3	4	3	5	< 0.0001	HS
10 week	0	0	1	1	0	1	< 0.0001	HS

HS: Highly Significant



**Fig 1:** CASE 6 OF TEST GROUP (a) Pre-operative X-ray (b) X-ray at 1<sup>st</sup> week (RUSH-15; VAS-4) (c) X-ray at 6<sup>th</sup> week (RUSH-24; VAS-3) (d) X-ray at 10<sup>th</sup> week (RUSH-30; VAS-0)



**Fig 2:** CASE 4 OF CONTROL GROUP (a) Pre-operative X-ray (b) X-ray at 1<sup>st</sup> week (RUSH-12; VAS-5) (c) X-ray at 6<sup>th</sup> week (RUSH-19; VAS-4) (d) X-ray at 10<sup>th</sup> week (RUSH-24; VAS-1)

## Discussion

Intertrochanteric fracture is one of most commonly treated fracture by a Orthopaedic Surgeon, the incidence of Intertrochanteric fracture is high usually in elderly people mainly after the age group of 60 years and more commonly in female because of postmenopausal osteoporosis [7]. The intertrochanteric fracture has to be surgically fixed as soon as possible if there is no contraindication for surgery. Once the surgery is done the patient should be mobilized as soon as possible to prevent the complications. Calcitonin helps to prevent the resorption of the bone especially helpful in osteoporotic patient and as intertrochanteric fracture are more common in elderly osteoporotic fracture. We did a study to assess the role of calcitonin in early fracture healing of intertrochanteric fracture treated surgically and also the analgesic effect of calcitonin.

In present study 40 patients were included and were randomly distributed in 2 groups 20 each. One group treated with salmon calcitonin intramuscular salmon calcitonin injection 100 IUOD till POD-7. After POD-7 the patients are administered with intranasal calcitonin for 3 months. And other control group placebo was given and the pain assessment using VAS scale and fracture healing assessment was done using RUSH score.

## Fracture Healing

In the present study within the interventional group, there was significant improvement in the RUSH score over period of 6 weeks and 10 weeks the p value <0.0001 showed statistical significance showing that there was fracture healing. Even in the control group the RUSH score calculated on 6th week and 10th week using WILCOXEN test and the p value <0.0001 shows that the value or statically significant denoting that there was improvement in RUSH score indicating fracture healing.

To compare the rate of fracture healing between the interventional group and the control group on basis of RUSH score, MANN-WHITNEY TEST was used. The minimum Rush score in interventional group at 1st week was 14 whereas in control group was 12 and maximum score in interventional group was 16 and control group was 14.

The minimum Rush score in interventional group at 6th week was 23 whereas in control group was 18 and maximum score in interventional group was 26 and control group was 21. The minimum Rush score in interventional group at 10th week was 29 whereas in control group was 23 and maximum score in interventional group was 30 and control group was 28.

This test signifies that the rate of fracture healing assessed using RUSH score at 1st, 6th and 10th in interventional group was significantly more when compared to control group as p value was <0.0001.

In a study conducted by Huusko TM, *et al.*, to assess the role of intranasal calcitonin in management of hip fracture in 260 geriatric patients depending upon pain, loss of bone, recovery and no. of days hospital stay and fusion of hip fracture in those who underwent fusion surgery using a screw or nail. After 90 days post procedure of intranasal calcitonin 200 IU, median pain was significantly reduced in calcitonin treated group while other parameters were comparable. Fusion was seen in 84% of group treated with calcitonin and 63 percent in placebo group. They concluded that intranasal calcitonin may be helpful for patients with hip joint fractures but to confirm clinical significance more studies need to be conducted having more patient & longer follow up period & increased dose of calcitonin [9]. Even in our study the rate of fracture in calcitonin group was significantly more as compared to control group.

Karachalios T, *et al.* conducted a study in 50 women between 70-80 years of age to assess the role calcitonin in averting bone loss after a fracture around hip joint and decrease the relativity of fracture in the same patient. divided randomly in two groups, group 1 received calcitonin while group 2, placebo. The level of alkaline phosphatase (ALP) and osteocalcin was assessed on 15th day post trauma and 90th day post trauma which showed significant increase in its level, the level of urinary excretion of c-telopeptide was

assessed on 15th, 45th & 90th days post trauma which showed less in group 1 than calcitonin group which signifies bone turnover rate and in group 1 there was documentation of reduced level of urinary hydroxyproline on 15th, 45th & 90th post trauma day. Group 1 had significant increase in mineral density of bone in all recorded areas except in one region that is greater trochanter done after 90 days & 365 days post-surgical intervention. The patients were observed for 4 years clinical to see for new fracture, 5 patient in group 2 had fresh fracture around the hip joint among 5 four patient had fresh fracture on opposite side of the old fracture. The result of this study showed that calcitonin has significant role in reducing acute bone loss in patient who have sustained fracture around the hip joint and also reduces the chance or probability of new fracture in same or opposite hip in geriatric patient <sup>[4]</sup>.

In 3rd study conducted by Pagonis TA, *et al.*, the role of calcitonin was compared to bisphosphonates in treatment of spinal fracture in osteoporotic patients treated conservatively. Group 1 was given calcitonin in combination with calcium and group 2 was given bisphosphonates. The patients were assessed using quality of life questionnaire of the European foundation for osteoporosis. The study signified that use of calcitonin causes early fracture union early stopping of analgesic drugs early mobilization without the brace. Calcitonin is helpful in fracture consolidation in patient in spinal fracture due to osteoporosis and indirectly improves the quality of life <sup>[6]</sup>.

From all the above studies we can infer that the calcitonin has a significant role in fracture healing especially in old age <sup>[10]</sup> patients having osteoporosis due to its bone resorption inhibiting property, even in the current study the patient treated with calcitonin had a faster rate of fracture healing as compared to placebo group.

## Pain

In present study in interventional group when the intensity of the pain at 1st week was compared it with that 6th week and 10th week using WILCOXEN TEST the intensity of the pain has significantly reduced suggested by p value <0.0001. Even in the control group the intensity of the pain at 1st week was compared it with that 6th week and 10th week using WILCOXEN TEST the intensity of the pain has significantly reduced suggested by p value <0.0001 but the patient were not completely pain free.

The intensity pain as calculated by VAS score was compared at 1st week, 6th week & 10th week using MANN-WHITNEY test showed that the interventional group had a lesser intensity of pain as compared to the control group as showed by the p value which is less than 0.0001. So helping in early mobilization of the patients.

In a study conducted by Lyritis GP, *et al.* clin j pain to evaluate the role of calcitonin suppositories in reducing pain there study had 40 patients, 8 were men and 32 were postmenopausal women who had a vertebral fracture<sup>11</sup> as complication of osteoporosis which were non traumatic<sup>12</sup> they divide the patients randomly in to 2 group one group was given with calcitonin suppository and other group was given placebo daily once for 28 days. All the patients were permitted to take Paracetamol 500mg tab maximum up to 6 tabs. The pain was assessed from day 1 today 28 using vas scale by applying direct pressure on the fractured vertebra the pain was also assessed at different locomotor of function during walking standing sitting and taking bed rest, The result showed that the patient treated with calcitonin suppositories had statistically significant reduction of the pain all p values

<0.001 assessed by VAS and pain-meter device.

## Conclusion

The rate of fracture healing as assessed using RUSH score was faster showing early fracture union, complete consolidation of fracture and early disappearance of fracture line and reduced intensity of pain in calcitonin treated group, Hence, therapy of combined intramuscular and intranasal salmon calcitonin given post operatively is useful for early healing and repair of intertrochanteric fractures and offers immediate and lasting pain relief.

However, further studies with larger population and longer follow-up period will be needed in the future before Salmon Calcitonin can be added to the wide spectrum of treatment available in the management of Intertrochanteric fractures.

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