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Original Article

Effect of Denosumab Injection in Early Union and Consolidation of Callus in Aseptic Tibial Shaft Non-union

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ABSTRACT

Fractures of the tibial shaft is one of the most common fractures than any other long bone fractures in the human body. Surgical treatment offers better functional outcome than a conservative management. Reamed intramedullary interlocking (IMIL) nailing is the treatment of choice for most of the closed tibial shaft fractures. Despite after a good surgical fixation non-union still persists after reamed IMIL nailing. Plate augmentation and bone grafting with nail in situ was found to have superior results and union rates than any other methods, but the average union time was almost 3 to 5 months. To enhance faster union and recovery here we have used Injection Denosumab 60 mg Sc post operatively during follow up. So, the aim of the study is to find the efficacy of injection Denosumab in enhancing early union and consolidation of callus. It is a comparative prospective study involving 43 patients treated for aseptic non-union of tibial shaft fractures following reamed intramedullary interlocking nailing between 2020 and 2023. All the patients treated by reamed intramedullary interlocking nailing who met the inclusion and exclusion criteria were included in the study. Group A was managed with plate augmentation and bone grafting following non-union IMIL nailing and Group B was managed with Plate augmentation bone grafting with Injection Denosumab Sc post operatively. Both the groups were followed up post operatively for period of one year. Total of 43 patients were included in the study. The average duration of union in GROUP A -14.82 weeks and in GROUP B-9.45 weeks. Excellent results were obtained in both the groups. There was no complication such as malunion, non-union, implant loosening, nerve palsy, infection and plate/IMIL nail breakage. Augmentation plating, decortication and autogenous iliac crest bone grating is a better treatment option compared to exchange nailing in case of tibial shaft aseptic non-union following IMIL nailing. Using injection denosumab 60mg Sc postoperatively after plate augmentation and bone grafting offers early union and early consolidation of callus.

Keywords: Tibial Shaft Fractures; Intramedullary Interlocking Nailing; Plate Augmentation; Bone Grafting

INTRODUCTION

Fracture of the tibia shaft is one of the most common fractures than any other long bone fractures in the human body[1]. First reason being the subcutaneous position of the bone in the lower limb. Among all the tibia fracture types AO OTA type 42-A1 is the most common fracture type constituting around 34%[2]. Apart from being most common fractured bone in the body it's the commonest bone going for non-union. The prevalence of tibial shaft non-union is found to be 2% to 10% of all tibia fractures and is higher in high velocity injuries and open fractures[3].

There are various reasons for tibia shaft to go for non-unionlike high velocity injuries with significant comminution, bone loss and fracture gaps, extensive soft tissue stripping with neurovascular deficit, infection following fixation, smoking, poor nutritional status, diabetes mellitus, renal insufficiency, Vitamin D deficiency, inadequate blood supply, medications like steroids, nsaids, opiates, poor fracture fixation /inadequate immobilization and Iatrogenic injury to soft tissues[4].

Adequate blood supply is important factor for fracture union to occur[5,6]. Compared to other long bones in the body the tibia with subcutaneous border has poor blood supply[7].

Conservative management of the tibial shaft fractures with cast and functional bracing results in high incidence of malunion and malalignment[8]. Surgical management with intramedullary interlocking(IMIL) nailing offers good functional outcome compared to conservative management[8]. But the incidence of non-union still persists after surgical management of tibial shaft with reamed intramedullary interlocking nailing.

There are various treatment options available for non-union of tibial shaft fractures following IMIL nailing like Electrical stimulation, Low intensity pulsed ultrasound, extracorporeal shock wave therapy, Injection of Bone marrow aspirate, Platelet rich plasma injection and operative procedures like bone grafting, Nail dynamization, external fixation, Limb reconstruction system fixation, Fibular osteotomy, Exchange reamed IMIL nailing, Illizarov fixation and finally Plate augmentation with Bone grafting.

Open reduction, decortication of ends with bone grafting was the old standard method used in non-union of tibia shaft fracture after intramedullary interlocking nailing. On the other hand, plate augmentation with bone grafting was found to have early union rates compared to reamed exchange nailing of tibia in IMIL nail non-union[9].Other non-invasive methods like bone marrow injection in non-union site has shown promising results[10,11] but the union rates are not as good as plate augmentation and bone grafting.

In search of early union and faster recovery from non-union we have used bisphosphonates and teriparatide. Teriparatide effectively reduces the osteoclastic activity at fracture site there by promoting early non-union and callus formation[12].

In our study as an alternate to Injection teriparatide we have used Injection Denosumab along with plate augmentation and bone grafting in non-union following reamed intramedullary interlocking nailing tibia. Denosumab is a human monoclonal IgG2 antibody genetically engineered in hamster ovary cells. Denosumab binds to RANKL preventing RANKL from activating its receptor, RANKL on the surface of osteoclasts and their precursors. This acts to inhibit osteoclast function thereby decreasing bone resorption.

Aim of our study is to find the efficacy of Denosumab in promoting early union and consolidation of callus in Plate augmentation and bone grafting following non-union secondary to reamed IMIL nail in Tibia shaft fractures.

MATERIALS AND METHODS

It is a comparative prospective study involving 43 patients treated for aseptic non-union of tibial shaft fractures following reamed intramedullary interlocking nailing between 2020 and 2023 at a private clinic in Chennai, Tamil Nadu, India. All the patients treated by reamed intramedullary interlocking nailing were identified.

- Inclusion criteria
  - Age between 18 yrs -60 yrs.
  - Non-union following Tibial shaft fractures treated with reamed IMIL nail without distal one third fibula fracture.
  - Closed tibia shaft fractures without neurovascular deficit under AO-OTA type 42A and 42B treated by reamed IMIL nail.
  - Hypertrophic and oligotrophic non-union following reamed IMIL nailing.
- Exclusion criteria
  - Age greater than 60 yrs and less than 18 yrs.
  - Infected non-union and Atrophic non-union.
  - Gap non-union >1cm.
  - Non-union secondary to open reduction and internal fixation with plate osteosynthesis.
  - Non-union following conservative management/ illizarov fixation/External fixation/LRS (limb reconstruction system).
  - Non-union secondary to open fractures treated with IMIL nail.
  - Tibia shaft fractures associated with distal one third fibula/femur fractures/ankle fractures either in the ipsilateral limb or contralateral limb.
  - Osteoporotic and pathological fractures.
  - High energy fracture with significant comminution (AO-OTA type 42C) treated by IMIL nail.
  - Open fractures with bone loss and neurovascular deficit treated by IMIL nail.
  - Smoker/poor nutritional status.
  - Diabetes mellitus / Vitamin D deficiency patients.
  - Patients on medications like steroids, Nsaids, opiates etc.
  - Inadequate stabilization/mobilization.
  - Pre-existing knee/hip/ankle stiffness/deformity in the ipsilateral or contralateral limb.
  - Treated by different surgical team.

All the patients who met the inclusion and exclusion criteria were taken up for the study. All the patients were treated by same surgical team. All the patients were categorised in to two groups, Group A-Patients undergone Plate augmentation and bone grafting in non-union tibial shaft fractures treated by reamed IMIL nail. Group B-Patients undergone Plate augmentation+ Bone grafting+ Denosumab injection in non-union tibial shaft fractures treated by reamed IMIL nail. We used AO-OTA classification on the initial x rays to classify tibial shaft fractures. Non-union was considered when the radiograph showed non-union between three and six months after initial treatment of tibial shaft fractures. The indication of surgical treatment was based on clinical signs of Pseudoarthrosis (PSA) with or without mobility at fracture site and radiological absence of bony union after three and six months of initial treatment.

All the patients underwent blood tests ESR, CRP, WBC preoperatively to exclude non-union secondary to infection.

The surgical treatment consists of Osteosynthesis with screw plate construct with cortico-cancellous auto-graft from the ipsilateral iliac crest. Through antero- lateral approach 1cm lateral to tibial crest non-union site was exposed. Both the ends of the non-union site are decorticated until there is some amount of bleeding, excess callus in the surrounding bone and tissue removed. Appropriate end to end reduction done and fixed with 4.5mm dynamic compression plate. Fibular osteotomy done if there is difficulty in getting complete reduction. After fixation non-union site is filled with cortico-cancellous bone graft from iliac crest. A swab was taken intraoperatively from non-union site to exclude infected non-union.

Post operatively dressing done on 2nd, 5th and 9th POD and suture removal done between 12 – 14 days. The patient was allowed to walk with non-weight bearing mobilization with walker from the second POD. Partial weight bearing started as soon as

Tolerated until union was achieved. Each patient was followed once in two weeks up to six weeks, then once a month up to 6 months and then every 6 months. Functional and radiological evaluation were done in monthly visits till union is achieved. Randomly one group of patients (GROUP B) were given 2 doses of denosumab injection 60mg subcutaneously after 2 weeks and 4 weeks after follow up the other group (GROUP A) was control group without denosumab injection. Both the groups were followed up regularly for clinical and radiological assessment till 1 yr. Radiological union was considered when there was union in three cortices in Ap, Lateral, and Oblique views. To assess the outcome of aseptic non-union after surgical treatment, we used modified ASAMI classification (Table 1).

Table 1: ASAMI classification

	Bone result	Functional result
Excellent	Bone union, No infection deformity <7% LLD (Lower limb discrepancy) <2.5cm	Ability to perform previous activities of daily living (ADL) no pain or mild pain No limp no soft tissue sympathetic dystrophy knee or ankle joint contracture<5% Loss of ankle or knee motion<15%
Good	Bone union failure to meet one of the other criteria	Almost all ADL with minimal difficulty No pain or mild pain, failure to meet one of the other criteria
Fair	Bone union failure to meet two of the other criteria	Most ADL with minimal difficulty No pain or mild pain, failure to meet two of other criteria
Poor	Non-union or refracture, failure to meet three of the other criteria	Significantly limited ADL Significantly pain requiring narcotics, failure to meet three of other criteria

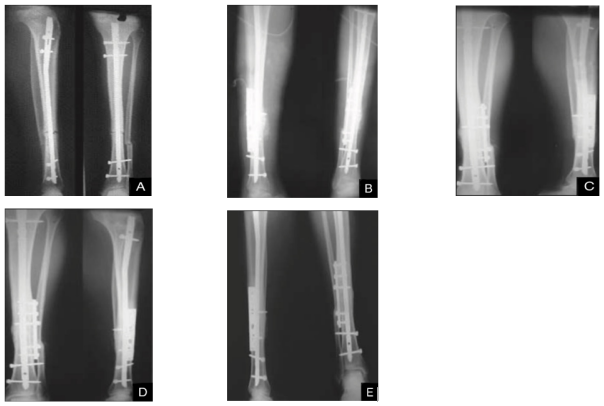

Fig. 1: (A) Tibia non-union after reamed IMIL nailing (B) Augmentation plating with autogenous iliac bone graft (C)Union progression at 3 months (D) 6 months post-operatively(E) and solid union with remodelling at 36 months post-operatively

RESULTS

Total of 43 patients were included in the study and these patients were divided into two groups as mentioned in the materials and methods. The average follow-up period was 27.16 months in both the groups. The average duration of union in GROUP A-14.82 weeks and in GROUP B- 9.45 weeks. The results of the study are summarised in Tables 2 and 3. All the patients in both the groups had bony union with excellent outcomes as per modified ASAMI scoring system. The preop x ray showing non-union after IMIL nailing and further follow-up x rays after union is shown in Figure 1. There was no complication such as malunion, non-union, implant loosening, nerve palsy, infection and plate/IMIL nail breakage.

DISCUSSION

Tibial shaft fractures are the most common fractures among all long bone fractures in the human body. Reamed intramedullary interlocking nailing is the popular treatment of choice for most of the tibial shaft fractures. Although proper reduction and relative stability is offered by reamed intramedullary interlocking nailing, non-union do occur sometimes [13]. Non-union of the tibial shaft fractures impose financial burden to patients and two-fold increase in health care cost compared to patients without non-union [14]. Tibial shaft non-union if not treated early can result in secondary changes to the knee and ankle joint like stiffness resulting in reduced range of motion. Moreover, early treatment and early recovery can provide a better functional outcome.

Table 2: Group A- Tibial shaft non-union post reamed IMIL nailing treated with Augmentation plating+ Decortication+ Autogenous illiac crest bone grafting

No	Sex	Age	Site	Bone	Non-union type	Time of Non-union (months)	Bone Grafting	Time of Union (weeks)	Follow-up in months
1	M	42	RT	T	H	8	G	12	24
2	M	35	LT	T	O	6	G	14	30
3	M	38	RT	T	O	10	G	14	36
4	F	54	RT	T	H	10	G	17	42
5	F	24	LT	T	O	9	G	16	36
6	M	26	RT	T	H	10	G	18	12
7	M	29	LT	T	O	6	G	26	24
8	F	31	RT	T	H	9	G	12	24
9	M	34	RT	T	O	7	G	16	30
10	M	36	RT	T	H	10	G	20	24
11	M	23	LT	T	O	8	G	12	28
12	F	57	LT	T	O	7	G	16	18
13	F	54	LT	T	O	6	G	11	30
14	M	37	RT	T	O	8	G	12	36
15	M	38	RT	T	O	8	G	14	24
16	M	48	RT	T	H	9	G	16	24
17	M	39	LT	T	O	10	G	16	18
18	M	29	RT	T	O	8	G	14	24
19	F	26	RT	T	O	7	G	16	36
20	M	43	RT	T	O	10	G	12	42
21	F	53	LT	T	O	8	G	16	12
22	M	56	LT	T	O	9	G	11	24
23	M	59	RT	T	O	8	G	10	30

Reamed exchange nailing is the procedure of choice for non-union after intramedullary nailing[15,16]. Earlier studies showed good results (96%-100%) following exchange nailing but later studies showed less favourable results following exchange nailing[17–21] in tibial shaft non-union. Better union and good clinical results are achieved by augmentation plating and bone grafting with the previous nail left in place. Ueng et al introduced the augmentation plating with bone grafting in the year 1997 and 1998 for non-union secondary to intramedullary interlocking nailing[22]. Although 100% results were obtained following plate augmentation and bone grafting, the average time of union was 3 to 5 months.

Using teriparatide for early union and consolidation of callus has shown promising results[13]. In our study we have used injection Denosumab as a new alternative to analyse efficacy of drug in early rate of union and early consolidation of callus following plate augmentation and bone grafting. Here we have compared two groups GROUP A only with plate augmentation+ bone grafting and GROUP B Plate augmentation+autogenous Bone grafting+ two dose Denosumab 60mg injection subcutaneously given post operatively after 2 weeks and 4 weeks of follow up.

In GROUP A, the average union time was 14.82 weeks whereas in GROUP B average union time was 9.45 weeks. It is evident from our study that early union and consolidation of callus occurs with use of Denosumab injection.

CONCLUSION

Augmentation plating, decortication and autogenous iliac crest bone grating is a better treatment option compared to exchange nailing in case of tibial shaft aseptic non-union following IMIL nailing. Though 100% union rates and excellent results are achieved using augmentation plating and bone grafting, the average time of union is delayed. With the use of Denosumab injection we can achieve early union and consolidation of callus thereby facilitating early mobilization and good quality of life.

Table 3: Group B - Tibial shaft non-union post reamed IMIL nailing treated with Augmentation plating+ Decortication+ Autogenous illiac crest bone grafting+ Denosumab 60mg subcutaneous injection

No	Sex	Age	Site	Bone	Non-union type	Time of Non - union (months)	Bone Grafting	Time of union (weeks)	Follow-up in months
1	M	21	LT	T	H	9	G	8	18
2	F	28	RT	T	O	10	G	14	28
3	M	32	RT	T	H	8	G	10	24
4	M	35	RT	T	O	9	G	9	30
5	M	33	LT	T	O	10	G	8	36
6	F	37	RT	T	O	9	G	12	42
7	M	45	RT	T	H	7	G	7	48
8	M	42	LT	T	O	8	G	9	36
9	F	47	RT	T	H	11	G	12	24
10	M	56	RT	T	O	10	G	10	12
11	M	55	LT	T	O	9	G	9	12
12	M	43	RT	T	O	10	G	9	18
13	F	42	RT	T	H	9	G	7	36
14	M	40	LT	T	O	8	G	8	38
15	M	31	RT	T	H	10	G	12	12
16	M	30	LT	T	O	7	G	8	36
17	M	28	RT	T	O	8	G	9	24
18	M	39	RT	T	O	10	G	10	24
19	F	56	RT	T	O	11	G	10	18
20	M	38	LT	T	O	10	G	8	24

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