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Evaluation of results of anabolic steroid injections in treatment of delayed union and non union of long bone fractures

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Abstract

The long-term complications of fractures both with or without treatment include delayed union, malunion, nonunion, infected non-union. Nonunion of the long bones fractures is a serious complication prolonging patient morbidity, time lost from work, and economic burden over family. Patients with non-union have significant disability and costs to the patient. Direct evidence of bone formation by Nandrolone Decanoate was given earlier by many. Anabolic process of protein synthesis, with new tissue formation, requires the action of anabolic hormones. Exogenous administration of these agents has been shown to maintain or increase lean body mass as well as directly stimulate the healing process through their anabolic and anti-catabolic actions. Our study aims to study efficacy of anabolic steroids in healing of non-union of fractures and recovery in delayed union. Patients in the age group of 20-80 years with confirmed clinical and radiological diagnosis of delayed and non-union and ready for follow up visits on regular basis were selected for study. Patients were thoroughly evaluated and assessed. Patients included in study were given intramuscular injection of Nandrolone Decanoate 50 mg once in every three weeks. Total period for administration of injection was 6 months with patients follow up at 3rd, 6th and 12th month. We studied 44 cases in the period of two years from December 2015 to December 2017. We found that transverse fractures (40%) commonly undergo non-union. In our study, 35 patients were managed with operative (79.5%) and 9 patients were managed with conservative management (19.5%). Twenty six cases (59%) had delayed union and 18 were of non union (41%). In our study the number of doses given to patients were between 3 to 7. In our study, 28 patients showed good results (63.6%), 4 showed satisfactory results (9.1%), 6 showed excellent results (13.6%), 6 showed no response (13.6%). In patients with application of RUST criteria for union, we observed gradual rise in accordance of healing of fracture with pre-treatment mean RUST value of 4.9, within 3 months of treatment RUST rose to 7.2. At 6 months of treatment mean RUST value was 9, and after 12 months mean RUST was 10.5. These observations were consistent with callus formation in our study. We concluded that delayed union and non-union of long bones can be treated conservatively. Patients treated with Nandrolone Decanoate 50 mg intramuscular once every three weeks showed positive results. This avoids multiple operative procedures like bone grafting. Multiple hospital admissions and long hospital stay was also avoided as patients were treated on OPD basis. Our intervention can be considered as a simple and short treatment course with satisfactory results reducing the economic burden on patients and their family. Nandrolone Decanoate can be considered a valid, economical and a non-operative alternative for patients of delayed union and non-union.

Keywords: non-union, delayed union, anabolic steroids, tibia

Introduction

In India, the availability of fracture healing therapies to the general public is limited. The infrastructure of the health system in India, involving both public and private sector does not provide adequate opportunity for rural and low-income inhabitants to access the needed care. The long-term complications of fractures both with or without treatment include delayed union, malunion, nonunion, infected non-union. Incidence of delayed union or non-union of fractures occurs in 5% to 10% of long-bone fractures. Early recognition of delayed or non-union improves outcome and prevents further anxiety and disability for the patient. Nonunion of the long bones fractures is a serious complication prolonging patient morbidity, time lost from work, and economic burden over family. Patients with non-union have significant

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disability and costs to the patient. Antonova *et al.* found the median total cost of care for a tibial nonunion to be more than twice the cost associated with a tibial fracture that goes on to uneventful union. Their management is time-consuming with frequent hospital admissions. These complications may lead to long-term dysfunction with chronic pain, disability and clinical depression. Treatment of non-union often is complex, needs coordinated involvement of multiple specialist like plastic surgeons, physician, physical and occupational therapist, psychiatrist but it also offers great reward because many of these patients have been significantly disabled for a prolonged period of time. Direct evidence of bone formation by Nandrolone Decanoate was given earlier by many. Farida Ahmad *et al.* found that Nandrolone Decanoate administered groups showed better fracture healing as a dense periosteal bone formation and prevention of the local osteoporosis [1].

On Nandrolone Decanoate administration, plasma calcium and phosphate fell significantly and there was a significant rise in the renal tubular reabsorption of calcium and a fall in the renal tubular reabsorption of phosphate and also there was a significant rise in radio calcium absorption. The results were consistent with the concept that Nandrolone exerts a significant positive effect on bone formation and that this results in a fall in the fasting plasma calcium level, and consequently calcium excretion (Need 1987) [2]

Anabolic process of protein synthesis, with new tissue formation, requires the action of anabolic hormones. Demling *et al.* Exogenous administration of these agents has been shown to maintain or increase lean body mass as well as directly stimulate the healing process through their anabolic and anti-catabolic actions [3]

This study aims to study efficacy of anabolic steroids in healing of non-union of fractures and recovery in delayed union and to reduce the economic burden over patients and family members.

Materials and Methods

We conducted a prospective clinical study on forty four patients in Department of Orthopaedics, Government Medical College and Hospital, Mumbai for the evaluation of effects of intramuscular anabolic steroid (Nandrolone Decanoate) in delayed union and non-union of long bone fractures. Ethical Committee approval and informed written consent was obtained from all the patients prior to the initiation of study. Patients of either gender in the age group of 20-80 years with confirmed clinical and radiological diagnosis of delayed and non-union and ready for follow up visits on regular basis were selected for study. Patients with gap non-union and uncontrolled medical illness (hypertension, renal and hepatic dysfunction) were excluded from the study. Patients were thoroughly evaluated and assessed. Evaluation of patients comprised of history of previous medical illness, any surgery, drug allergies and general physical examination. Basic blood investigations, radiograph of chest, ECG were performed. Patients included in study were given intramuscular injection of Nandrolone Decanoate 50 mg once in every three weeks. Injection was given on OPD basis with monitoring of the patient for at least 1 hour for any allergic reactions. Total period for administration of injection was decided for 6 months with patients follow up at 3rd, 6th and 12th month.

At each visit, patients were assessed clinically for tenderness (VAS scale), gait and abnormal mobility at fracture site. Blood investigations like liver function tests and renal function tests were done to assess the adverse effects of the drug. Radiological assessment was done with serial x-rays at

each visit. We also calculated range of movements at the joints adjoining the affected limb, and compared range of movement at the same joint of the opposite limb. All quantitative data was presented as mean \pm SD (standard deviation). The statistical software SPSS version 23.0 was used for the analysis and students test and chi square test was applied to calculate results.

We used RUST [4] system which is the only grading system available for tibia fracture. Previous research in successful radiographic criteria determined that that the RUST score should be based on the following: callus formation and fracture line visibility. RUST uses X-ray images to assign a numerical score to fractured tibia. A maximum score of 12 is achieved when the bone is fully healed and a minimum score of 4 is given for no healing. Scores are awarded based on callus formation and fracture line visibility at each of the four cortices of two orthogonal x-ray images: anterior, posterior, medial and lateral. Functional assessment done with the use of activities of daily living (ADL) score. Bone marrow density was measured before treatment and then at three, six and 12 months.

Results

We studied 44 cases in the period of two years from December 2015 to December 2017 and following observations are made. Population included in our study was between age group of 19 to 80 years of age with mean age of patients is 41 ± 16 years. Males were more 39 (89%) affected as compared to females in our study. All the long bones were studied. Sixteen cases of tibia (36.4 %), 14 cases of femur (31.8%), 5 patients of humerus (11.4%), 3 patients in whom both radius and ulna was involved (6.8%), 2 patients of radius (4.5%) and one patient each of radius, ulna, patella and metacarpal. Lower extremity cases (70%) were predominant in our study. In our study all type of long bone fractures, transverse, spiral, oblique, comminuted closed and open were included. Out of which, 18 cases were of transverse type (41%), 12 cases were comminuted (27%), 9 cases were oblique (20%), 5 cases were of spiral type fracture (11%). From our observations, we found that transverse fractures (40%) commonly undergo non-union. In our study of 44 patients, 35 patients were managed with operative (79.5%) and 9 patients were managed with conservative management (19.5%). Out of which 22 cases were treated with intramedullary interlock nail (50%), 8 cases were managed with plating (18%), 3 cases were stabilised with external fixator (6.8%), in one patient the fracture was fixed with cannulated cancellous screw (2.3%), 1 case fixed with K wire (2.3%). Patients operated with intramedullary interlock nail frequently (50%) resulted in non-union in our study. In our study, 26 cases (59%) had delayed union and 18 were of non-union (41%). Out of the 3 patients managed with external fixator, 2 had delayed union and 1 went into non-union. K wire fixation went into non-union; in intramedullary nailing group 11 patients showed delayed union and 11 showed non-union; in plate fixation 6 showed delayed union and 2 were of non-union; the case of screw fixation was of non-union. In 9 patients managed conservatively 7 showed delayed union and 2 showed non-union. In our study the number of doses given to patients were between 3 to 7. While 28 cases received 5 doses of intramuscular injection, 13 cases received 7 doses of injection, 2 cases received 3 doses of intramuscular injection, 1 case received 6 doses of intramuscular injection without any complications. In our study, 28 patients showed good results (63.6%), 4 showed satisfactory results (9.1%), 6 showed

excellent results (13.6%), 6 showed no response (13.6%). In patients with application of RUST criteria for union, we observed gradual rise in accordance of healing of fracture with pre-treatment mean RUST value of 4.9, within 3 months of treatment RUST rose to 7.2. At 6 months of treatment mean RUST value was 9, and after 12 months mean RUST was 10.5. These observations were consistent with callus formation in our study. In our study, on a 100 mm VAS scale with pre-treatment mean of VAS of 66, patient showed positive response with mean VAS after 3 months of 54, after 6 months VAS of 40 and after 12 months a VAS of 15. On comparison of range of motion of joint near to the fracture site with normal side, with pre-treatment mean ROM of 51. After treatment for 3 months, patients showed positive response with mean ROM score increased to 54, after 6 months mean ROM score rose to 64 and after 12 months again there was an increase in ROM score with mean of 70. The decrease in VAS score and increase in mean ROM score was found to be statistically significant. In our study, on comparison of activities of daily living (ADL) by Katz index, pre-operative index mean of 4.7, after 3 months of treatment ADL showed positive response with mean value of 4.77, after 6 months of treatment mean ADL of 5.2 and after 12 months mean ADL was 5.33, with statistical P value significant. The pre-treatment BMD of the patients was -0.382, after 3 months of treatment mean BMD was -0.259 (positive response), at 6 months mean BMD was -0.034 and at 12 month follow up mean BMD was of 0.088. This change in BMD value was found to be statistically significant.

Discussion

Fracture healing is a natural process in which orthopaedicians serves a part of fixation which is either by conservative or operative management. Any kind of pathology which delays this natural process of healing will lead to complications of healing i.e. delayed union and non-union. These complications cause lot of morbidity to patient and family members. Lyritis *et al.* from their double-blind randomised controlled trial showed better mobility and less pain in people with vertebral fractures after treatment with anabolic steroids compared with a vitamin D analogue, alphacalcidol [5].

Iwakura *et al.* [6] found on histological examination, flow cytometry revealed that the adherent cells were consistently positive for mesenchymal stem cell related with the presence of lineage-specific induction factors, the adherent cells differentiated in vitro into osteogenic, chondrogenic and adipogenic cells. This suggested that non-union tissue plays an important role during the healing process of non-union by serving as a reservoir of mesenchymal cells that are capable of transforming into cartilage and bone forming cells.

The study of Pärssinen M. *et al.* [7] on the effect of supra physiological doses of anabolic androgenic steroids (AAS) on collagen metabolism and the changes reflect the alterations in muscle, bone, and tendon collagen metabolism. High doses of AAS were suggested to enhance tissue collagen metabolism on the basis of increased type III collagen synthesis and elevated HP/LP ratio during the steroid administration period. These studies form the basis of our study for the use of anabolic steroid in context of bone forming agent.

The osteoblastic activity was assessed by measuring the serum alkaline phosphatase levels and locally in the callus by measuring the alkaline phosphatase activity, by Nilsson and Granstrom [8] The high levels of serum alkaline phosphatase and the callus alkaline phosphatase activity in the experimental group in the study demonstrated a better fracture

healing than that in the control group. Frankle and Borrelli [9] reported high levels of calcium in the healing callus with the use of anabolic steroids. Farida Ahmad *et al.* [11] observed that the Nandrolone treated animals achieved higher levels of callus calcium than the control group, which showed a better bone mineralization activity. Anabolic steroids have also been shown to trigger the release of the transforming growth factor beta by fibroblasts, which stimulate the bone formation in the granulation tissues.

R Nandra *et al.* [10] in his study observed peak age of non-union to be 30 to 40 years and more common in males. The incidence in males was bimodal, which mirrors the incidence of fractures overall peaking at 25 to 30 years and then again at 80 years of age. In our study of 44 patients with mean age of patients was 41 years with a range from 25 to 57 years, males showed preponderance with 39 (89%) and 5 (11%) females.

R Nandra [10] study also showed that incidence of tibia fracture was 26/100000 year. Those treated with reamed nail had 1.6–8% non union rate, unreamed nail had 11%, extra medullary plate had 1% while those treated with conservative cast had a non union rate of 0 to 5%. In our study, patients treated with intramedullary nailing 11 showed delayed union and 11 showed non-union; in plate fixation 6 showed delayed union and 2 were of non-union. In 9 patients managed conservatively, 7 showed delayed union and 2 showed non-union.

Tidermark *et al.* [11] (2004) compared anabolic steroid injections every three weeks for six months and daily protein supplementation versus daily protein supplementation alone, in 40 women who were followed up for one year post-surgery. In our study we used intramuscular Nandrolone Decanoate 50 mg once in every three weeks for convenience of administration of drug and to avoid the side effects of the drug.

Hedstrom *et al.* [12] reported that three participants (9.4%) had side effects (hoarseness or increased facial hair) of anabolic steroids. Tidermark [11] reported nearly complete compliance with the administration of the anabolic steroid injection. Need² gave 50 mg of Nandrolone Decanoate every third week for one year. He observed a high incidence of hoarseness. In our study, we did not observe any side effects in patients taking drug.

Hedstrom 2002, observed patients at 3, 6, 9, and 12 months with study period of 12 months, data analysed was from 6 and 12 months. In our study, Intramuscular injection of 50 mg Nandrolone Decanoate once every 3 weeks was given under our observation with patients and observed for 1 hour for any allergic reactions. Patients were followed for assessment at 3, 6 and 12 months. We gathered information of patients from pre-treatment period and at 3 months, 6 months, 12 months.

In the study by Hedstrom (2002) VAS value of control group at 6 months was 15, anabolic group was 3.5, and at 12 months in control was 5 and in the anabolic steroid group was 6.5 with range of (0 to 41) 0.8

In our study we observed course of the pain on treatment with VAS scale (0 = no pain and 100 = severe pain). Patient's VAS was recorded before treatment and at 3, 6 and 12 months after treatment. We observed fall in the severity of pain with mean VAS score before treatment of 66, at 3 months of 54, at 6 months of 40, and at 12 months post treatment, a VAS of 15 ($p = 0.01$).

We also compared pre-treatment and post treatment range of motion of major joint near the affected site. We found mean ROM score before treatment was 50 and at 12 months follow up was 70. These values were found to be statistically

significant.

As there is no general consensus about the callus formation and union of the all long bones (Bhandari M 2002) [13] we used RUST criteria for fracture healing, with RUST range (4=no callus, 12=complete union).

Sandra Fiset [4] who carried out validation study on RUST showed minimum value of 9 of RUST for union. Litrenta J *et al.* [14] showed that majority of reviewers assigned union for a standard RUST of 9 and a modified RUST of 11, and >90% considered a score of 10 on the RUST and 13 on the modified RUST united. Perlepe *et al.* [15] showed reproducibility of RUST for other long bone fractures.

In our study, we observed gradual rise in accordance with healing of fracture and callus formation with pre-treatment mean RUST value of 4.9, at 3 months of treatment, mean RUST was 7.2, at 6 months mean RUST value was 9, and after 12 months mean RUST were 10.5.

In study of Hedstorm *et al.* [12] mean katz index was compared at 6 months and 12 months, with mean value at 6 months of 6 and at 12 months mean of 6. Tidermark *et al.* [11] also used katz index in study with positive results in Nandrolone group in recovery.

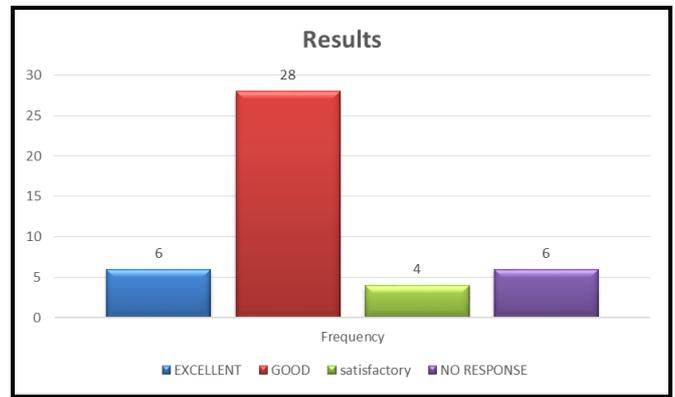
In our study, mean katz index before treatment was 4.70; at 3 months of treatment was 4.77, at 6 months was 5.20, and at 12 months of treatment was 5.3250 with p value of 0.01 suggesting that this difference in Katz Index was statistically significant.

Need [2] also found positive results on BMD with Nandrolone therapy. There was a rise in forearm mineral density from 285 ± 14 mg/ml to 294 ± 14 mg/ml ($P < 0.001$). Johansen JS [16] also showed in the Nandrolone Decanoate treated group that the fat corrected bone mineral content in the proximal part of the distal forearm (measured by single photon absorptiometry) showed a significant increase of 3% compared with placebo (p value < 0.01), and the same tendency was seen in the bone mineral content of the distal part of the distal forearm and density of the lumbar spine (measured by dual photon absorptiometry). Hedstorm (2002) also found that the anabolic steroid group, treated with a lower dose of Nandrolone Decanoate than in earlier studies, lost less BMD than the control group, particularly in the distal femur and proximal tibia which are areas with mostly trabecular bone. There were also positive effects on BMD in the femoral diaphysis, which is mostly cortical bone, on the injured side after both six and 12 months.

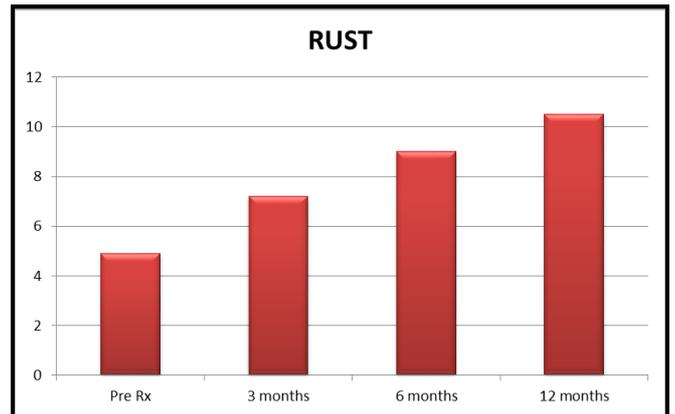
In our study, we used bone mineral density as a marker for bone mineral content, positive effects in correlation to BMD were reported by above authors in previous studies. In our patients, the observations made with respect to BMD showed positive results with pre-treatment mean for BMD of -0.382, which showed a positive response on treatment with drug with mean BMD at 3months of -0.259, at 6months of -0.034, and at 12 months of 0.0875. These values were found to be statistically significant.

Table 1: Rust Score

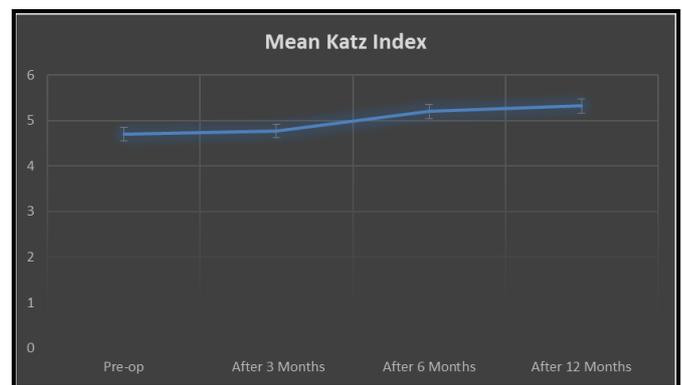
Radiographic criteria		
Score per cortex	Callus	Fracture line
1	Absent	Visible
2	Present	Visible
3	Present	Not visible



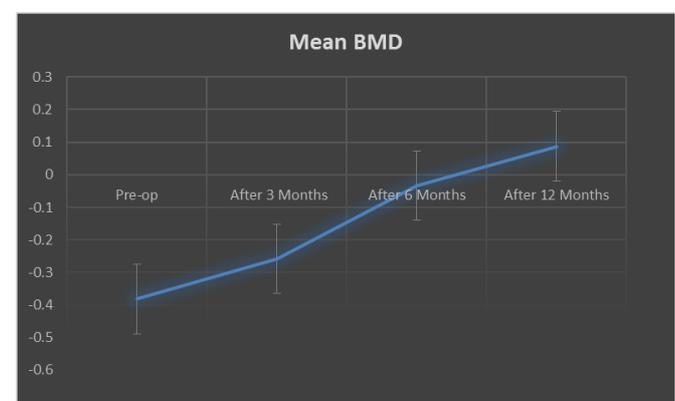
Graph 1: Results



Graph 2: Rust



Graph 3: Katz Index



Graph 4: BMD

Conclusion

From our study, we concluded that delayed union and non-union of long bones can be treated conservatively. Patients treated with Nandrolone Decanoate 50 mg intramuscular once every three weeks showed positive results. This avoids multiple operative procedures like bone grafting. Multiple hospital admissions and long hospital stay was also avoided as patients were treated on OPD basis. Our intervention can be considered as a simple and short treatment course with satisfactory results reducing the economic burden on patients and their family. Nandrolone Decanoate can be considered a valid, economical and a non-operative alternative for patients of delayed union and non-union.

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