National Journal of Clinical Orthopaedics

ISSN (P): 2521-3466
ISSN (E): 2521-3474

www.orthoresearchjournal.com
2019; 3(1): 79-84
Received: 16-11-2018
Accepted: 20-12-2018

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Autologous bone graft vs synthetic bone graft in treatment of non-union in long bones

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DOI: https://doi.org/10.33545/orthor.2019.v3.i1b.17

Abstract
Introduction: Long bones fractures affect almost all the age groups, including children, youth as well as elderly and postmenopausal women. In epidemiological studies its annual incidence has been found to be close to 1%, with slightly higher incidence in men as compared to women. These fractures are managed both conservatively as well as surgically and heal over due course of time. However, an estimated 5 to 10% of these fractures do not heal within a normal period and are classified as delayed or nonunion fractures. Nonunion is defined as a fracture that has not healed in expected time and there is cessation of physiological process of healing and has not shown any progressive visible radiological sign of healing.
Materials and Methods: This is a prospective randomized controlled study. It comprises two groups each having 22 patients. In one group autologous bone graft was used and in the other group synthetic bone graft was used. The maximum follow up was 9 months patients were assessed clinically and radiologically
Result: It was found that synthetic bone graft group of the patients have shown better union rates as compared to autologous bone graft clinically and radiologically after 9 months followup.
Conclusion: synthetic bone graft has yielded better results than autologus bone graft.

Keywords: autologous bone graft, synthetic bone graft, hydroxyapatite

Introduction

Long bone fractures are most common types of fractures following fractures of hands and the feet [1]. They affect almost all the age groups, including children [2], youth as well as elderly [3, 4] and postmenopausal women [5]. In epidemiological studies its annual incidence has been found to be close to 1%, with slightly higher incidence in men as compared to women. These fractures are managed both conservatively as well as surgically and are healed over due course of time. However, an estimated 5 to 10% of these fractures do not heal within a normal period and are classified as delayed or nonunion fractures [6, 7].

The development of non-unions depends on several factors, such as energy-level of trauma, type of fracture, soft tissue involvement, type of applied treatment, and various endogenous factors [9-11]. The development of a nonunion generally is associated with stiffness of surrounding joints and disability of the affected limb [12, 13]. Treatment of nonunion cases is a challenging task for the orthopedic surgeons. The foundation of treatment for nonunion lies on provision of mechanical and biological support at the affected site.

Fracture stabilization and immobilization is frequently used with the other treatment modalities that provide biological support to the fractured bone. Biological support includes materials that could be served as a source of osteogenic cells (osteogenesis), a stimulator of mesenchymal cells (osteoinduction), or a scaffold-like structure (osteoconduction).

The biological support process is achieved by use of bone grafts. A bone graft is a combination of undifferentiated stem cells, growth factors and structural lattice, each having a different role. Stem cells help in maintenance and repair of the tissue in which they are residing. A single stem cell can generate all cell types of that tissue while growth factors help in its growth and structural lattice provides a substrate for all these processes and helps to provide a shape and structure.

Autologous bone graft is generally considered the gold standard and the best material for

grafting because it contains several elements that are critical in promoting bone formation, including osteoprogenitor cells, the matrix, and bone morphogenetic proteins. The use of iliac crest autologous bone graft is widely considered as gold standard for a number of reasons, including osteogenic, osteoconductive, and osteoinductive properties and the lack of disease transmission or of immunogenicity [14-16].

The osteoconductive property of cancellous auto graft is related to the porosity of bone. The highly porous, scaffold-like structure of the graft allows host osteoblasts and host osteoprogenitor cells to migrate easily into the area of the defect and to begin regeneration of bone. Sources of cancellous bone are the iliac crest, the distal femur, the greater trochanter, and the proximal tibia. However, harvesting the autologous bone graft is associated with major drawbacks such as limited availability and variable quality of the graft, hematoma, infection, increased operative time and bleeding, chronic donor site pain, and additional cost [17]

Thus the development of synthetic materials with osteoconductive and osteoinductive properties that can eliminate the need for harvesting has become a major goal of orthopedic research Synthetic bone graft materials, *viz.* medical grade calcium sulfate minimize or eliminate the need for autogenous bone graft. Medical grade calcium sulfate is thought to function as an osteoconductive agent but also may have osteoinductive properties

Calcium phosphate ceramics (CaP ceramics) such as hydroxyapatite, tricalcium phosphate and biphasic calcium phosphate are some of the other synthetic graft materials that have potential of facilitating osseous healing. Moreover calcium phosphate cements, bioactive glass and polymethylmethacrylate (PMMA) bone cement have also been mooted as viable synthetic graft materials for the treatment of non-united long bone fractures.

Material and Methods

After ethical clearance from institutional review board this prospective issue study was carried out at department of orthopaedic surgery, Era's Lucknow medical college, Lucknow during January 2017 to June 2018. Patient was selected having Inclusion Criteria Patients over 18 years of age, with non-union of long bones, Not more than one previous operation at the non-union site. Patients with infected non-union and systemic diseases (unfit for surgery) were excluded.

Cases were recruited from Orthopaedics OPD after history taking, physical examination and X-ray of the affected part. The recruited cases were explained the purpose and relevance of the study. Those willing to volunteer were included in the study after informed and written consent.

Sex, age, body-mass-index (BMI), smoking status, time from trauma to index-operation and time from index-operation to follow-up were documented. The patients were then randomized into two groups one who received synthetic bone graft and other who received autologous bone graft.

All surgical procedures followed a specific operation-protocol: All patients received a single shot antibiotic preoperatively and anaesthesia was given. After exposure the non-union site was radically debrided and the medullary canal was opened to complete the freshening of the bone ends. The non-union site was then paced with adequate bone graft to achieve osseous contact.

Follow up of the patient was done at 1 month, 3 months, 6 months and 9 months.

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

The following Statistical formulas were used

1. **Mean:** To obtain the mean, the individual observations were first added together and then divided by the number of observation. The operation of adding together or summation is denoted by the sign Σ.
   The individual observation is denoted by the sign X, number of observation denoted by n, and the mean by $\overline{X}$.
   $$\overline{X} = \frac{\Sigma X}{\text{No . of observatio ns (n)}}$$

2. **Standard Deviation:** It is denoted by the Greek letter σ.
   $$\sigma = \sqrt{\frac{\Sigma (X - \overline{X})^2}{n}}$$

3. **Chi square test**
   $$\chi^2 = \sum \frac{(O - E)^2}{E}$$

Where O = Observed frequency
E = Expected frequency
Student 't' test: To test the significance of two means the

$$\text{Student 't' test was used } t = \frac{\overline{X}_1 - \overline{X}_2}{S\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

$$\text{Where } S^2 = \frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2}{N_1 + N_2 - 2}$$

Where $\overline{X}_1$, $\overline{X}_2$ are means of group 1 and group 2
N_1, N_2 are number of observation group1 and group 2
SD_1, SD_2 are standard deviation in group1 and group 2.

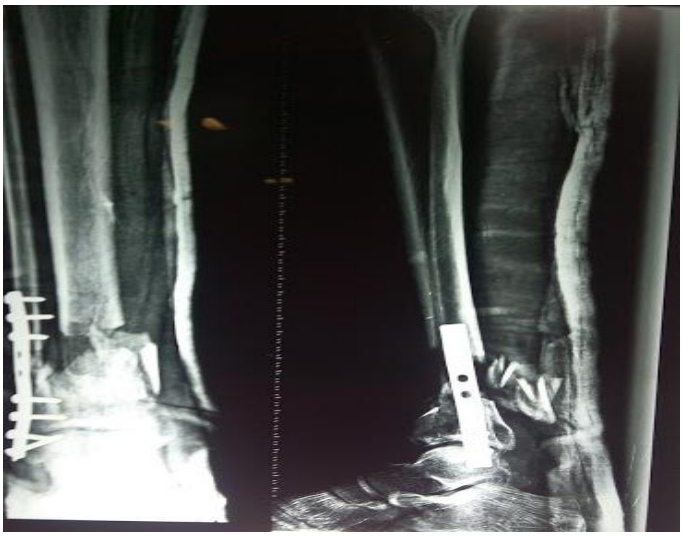

Fig 1: Autologous Bone Graft

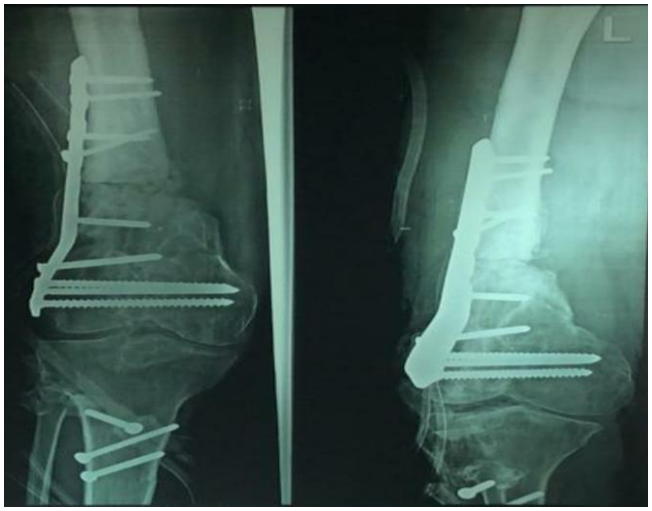

Fig 2: Synthetic Bone Graft

Results

The present study was carried out to compare the efficacy of autologous bone grafting against synthetic bone grafting in treatment of non union in long bones. For this purpose, a total of 44 patients with long-bone fractures of upper/lower extremity were enrolled in the study and were randomized into one of the two groups as follows:

Table 1: Group wise distribution of cases

S. N	Group	Description	No. of cases	Percentage
1.	A	Patients with long-bone fractures who received autologous bone graft	22	50
2.	B	Patients with long-bone fractures who synthetic bone graft	22	50

Table 2: Age wise distribution of cases in two groups

S. No	Age Group	Group A (n=22)		Group B (n=22)	
		No.	%	No.	%
1.	21-30 Years	0	0	2	9.1
2.	31-40 Years	11	50.0	10	45.5
3.	41-50 Years	7	31.8	3	13.6
4.	51-60 Years	4	18.2	4	18.3
5.	>60 Years	0	0	3	13.6
Mean Age±SD (Range)		43.05±8.31 (34-59)		44.23±12.02 (29-61)	

't'=0.379; p=0.706

On comparing the data statistically, there was no significant difference between two groups with respect to mean age (p=0.706).

Table 3: Distribution of cases in two groups according to mode of injury

S. N	Mode of injury	Group A (n=22)		Group B (n=22)	
		No.	%	No.	%
1.	Road traffic accident	15	68.2	16	72.7
2.	Hit by object	0	0	2	9.1
3.	Fall from height	4	18.2	4	18.2
4.	Slip	3	13.6	0	0

χ^2=5.032 (df=3); p=0.169

Statistically, there was no significant difference between two groups with respect to mode of injury (p=0.169).

Table 4: Distribution of cases in two groups according to limb involved

SN	Limb involved	Group A (n=22)		Group B (n=22)	
		No.	%	No.	%
1.	Lower	19	86.4	15	68.2
2.	Upper	3	13.6	7	31.8

χ^2=2.071(df=1); p=0.150

Though proportion of those having upper limb involvement was higher in Group B as compared to that in Group A yet this difference was not significant statistically (p=0.150).

Table 5: Comparison of Radiological Outcome in two study groups at different follow-up intervals

S. N	Characteristic	Group A (n=22)		Group B (n=22)		Statistical significance	
		No.	%	No.	%	χ^2	'p'
1.	One month					4.92	0.086
	Callus	13	59.1	18	81.8%		
	Infection	4	18.2	0	0		
	Non-union	5	22.7	4	18.2%		
2.	Three months					2.73	0.099
	Callus	13	59.1	18	81.8		
	No callus	9	40.9	4	18.2		
3.	Six months					2.44	0.118
	Callus	16	72.7	20	90.9		
	No callus	6	27.3	2	9.1		
4.	Nine months					2.44	0.118
	Callus	16	72.7	20	90.9		
	No callus	6	27.3	2	9.1		
5.	Radiological union at 9 months	15	68.2	18	81.8	1.09	0.296
6.	Time taken for radiological union	(n=15)		(n=18)		3.793	0.051
	3months	0	0	4	22.2		
	6 months	15	100	14	77.8		

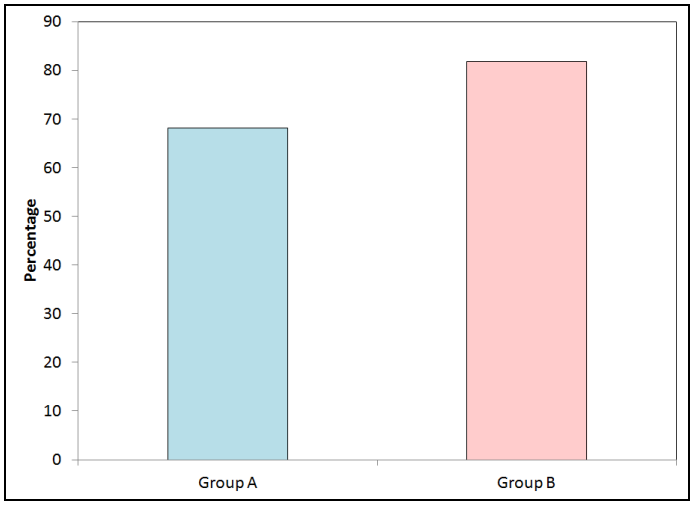

Fig 3: Union rate at 9 months in two study groups

Radiological evaluation at one month showed callus formation in 13 (59.1%) of Group A and 18 (81.8%) of Group B patients. In Group A, there were 4 (18.2%) cases showing infection and remaining 5 (22.7%) showed non-union whereas in Group B, remaining 4 (18.2%) cases showed non-union.

At three months evaluation too, callus formation was seen in 13 (59.1%) of Group A and 18 (81.8%) of Group B patients.

At 6 and 9 months, callus formation was seen in 16 (72.7%) of Group A and 20 (90.9%) of Group B patients.

At 9 months, radiological union was detected in 15 (68.2%) of Group A and 18 (81.8%) of Group B patients.

Statistically, there was no significant difference between two groups with respect to radiological outcome at any of the follow-up periods.

Table 6: comparison of pain between two study groups at different follow-up intervals

S. N	Characteristic	Group A (n=22)		Group B (n=22)		Statistical significance	
		No.	%	No.	%	χ^2	'p'
1.	1 month	4	18.2	0	0	4.400	0.036
2.	3 months	2	9.1	0	0	2.095	0.148
3.	6 months	0	0	0	0	-	-
4.	9 months	0	0	0	0	-	-

In Group A, at 1 and 3 months follow up intervals, a total of 4 (18.2%) and 2 (9.1%) patients complained of pain as compared to none of the patients in Group B. At subsequent follow-up intervals, none of the patients reported of pain in either of two groups. Statistically, a significant difference was observed between two groups at 1 month follow up interval only (p=0.036).

Table 7: Comparison of Weight bearing (lower limb) between two study groups at different follow-up intervals

S. N	Characteristic	Group A (n=19)		Group B (n=15)		Statistical significance	
		No.	%	No.	%	χ^2	'p'
1.	1 month					2.38	0.123
	No	7	36.8	2	13.3		
	Partial	12	63.2	13	86.7		
2.	3 months					2.38	0.123
	No	7	36.8	2	13.3		
	Full	12	63.2	13	86.7		
3.	6 months					4.18	0.124
	No	2	10.5	0	0		
	Partial	5	26.3	2	13.3		
	Full	12	63.2	13	86.7		
4.	9 months					0.435	0.510
	Partial	4	21.1	2	13.3		
	Full	15	78.9	13	86.7		

In Group A, a total of 19 and in Group B, a total of 15 patients had lower limb involvement.

At 1 month follow-up, in Group A, 7 (36.8%) patients showed no weight bearing while 12 (63.2%) showed partial weight bearing as compared to 2 (13.3%) in Group B showing no weight bearing and 13 (86.7%) showing partial weight bearing.

At 3 month follow-up, in Group A, 7 (36.8%) patients showed no weight bearing while 12 (63.2%) showed full weight bearing as compared to 2 (13.3%) in Group B showing no weight bearing and 13 (86.7%) showing full weight bearing.

At 6 months follow-up, in Group A, 2 (10.5%) patients showed no weight bearing, 5 (26.3%) showed partial and 12 (63.2%) showed full weight bearing as compared to 2 (13.3%) in Group B showing partial weight bearing and 13 (86.7%) showing full weight bearing.

At 9 months follow-up, in Group A, 4 (21.1%) patients showed partial weight bearing while 15 (78.9%) showed full weight bearing as compared to 2 (13.3%) in Group B showing partial weight bearing and 13 (86.7%) showing full weight bearing.

Statistically, group B Showed significatant results in term of weight bearing at 9 months.

Table 8: Comparison of ROM between two study groups at different follow-up intervals

SN	Characteristic	Group A (n=22)		Group B (n=22)		Statistical significance	
		No.	%	No.	%	χ^2	'p'
1.	1 month					5.48	0.140
	Full	1	4.5	5	22.7		
	Partial	12	54.5	13	59.1		
	Restricted	2	9.1	2	9.1		
	No	7	31.8	2	9.1		
2.	3 months					3.49	0.062

	Full	15	68.2	20	90.9		
	Partial	0	0	0	0		
	Restricted	0	0	0	0		
	No	7	31.8	2	9.1		
3.	6 months					5.71	0.057
	Full	15	68.2	20	90.9		
	Partial	5	22.7	0	0		
	Restricted	0	0	0	0		
	No	2	9.1	2	9.1		
4.	9 months					4.40	0.036
	Full	18	81.8	22	100		
	Partial	4	18.2	0	0		
	Restricted	0	0	0	0		
	No	0	0	0	0		

At one month, full to partial ROM was achieved in 13 (59.1%) of Group A and 18 (81.8%) patients of Group B. At three months follow up, 15 (68.2%) patients in Group A and 20 (90.9%) in Group B achieved full ROM. At 6 months follow-up, in Group A, 15 (68.2%) achieved full ROM, 5 (22.7%) partial ROM and 2 (9.1%) no ROM whereas in Group B, 20 (90.9%) achieved full ROM and remaining 2 (9.1%) and no ROM. At 9 months, all the patients in Group B achieved full ROM as compared to 18 (81.8%) in Group A. In Group A, at 9 months follow up, there were 4 (18.2%) patients who achieved partial ROM only. Statistically, the difference between two groups was significant at 9 months only (p=0.036).

Discussion

The present study was carried out in which hydroxyapatite was used as synthetic bone graft for treatment of non-union long bone fractures and was compared with autologous bone graft. For this purpose, a randomized study was carried out in which a total of 44 patients with non-union long-bone fractures were enrolled and randomized to one of the two study groups – a total of 22 (50%) were randomized to group that received synthetic bone graft while remaining 22 (50%) were randomized to group that received autologous bone graft.

In present study, signs of bone formation (callus formation) were earlier in synthetic graft group as compared to autologous graft group. At 9 months, radiological union was achieved in higher proportion (81.8%) of synthetic graft group patients as compared to autologous graft group (68.2%) but difference was not significant statistically. The synthetic bone graft showed a relatively earlier evidence of radiological union as compared to autologous bone graft. Moreover, it had fewer complaints like infection, tenderness and pain. With respect to clinical outcome too, synthetic graft showed those achievement of full weight bearing in 86.7% as compared to 78.9% patients in autologous graft group (78.9%). These findings suggested a better outcome in synthetic bone graft as compared to autologous bone graft both clinically as well as radiologically that too with relatively fewer complications.

There are limited studies comparing synthetic bone graft against autologous grafts for management of bone defects in general and non-union long bone fractures. However, most of the studies showing their use in bony defects or fracture healing have shown them to be promising and accompanied with fewer complications. Geesink *et al.* [18]. Error! Bookmark not defined. In their study showed success rate of 87.5% while evaluating the osteogenic activity of osteogenic protein-1 in bridging fibular defects at the time of tibial osteotomy for varus or valgus deformity of knee. Friedlaender *et al.* [19]. In their study on treatment of tibial nonunions found osteogenic protein-1 (OP-1) to be better as compared to auto graft both in terms of bone formation as well as in terms of fewer associated complications. In another study, Pieske *et al.* [20] Error! Bookmark not defined. compared demineralized bone matrix (DBM) against autologous bone grafts for treatment of un united long bones and found it to be promising without any significant complication. Tressler *et al.* [21] Error! Bookmark not defined. Too observed promising results for recombinant human bone morphogenetic protein-2 (rhBMP-2) when mixed with cancellous allograft on fracture healing when compared to iliac crest auto graft in the treatment of long bone nonunion.

The findings of present study thus showed that synthetic bone graft was not only well accepted but also offered fewer complications and a better radiological union rate than autologous bone graft. Thus showing that synthetic bone graft is a promising substitute that can tackle the complications associated with autologous graft retrieval too. Incidentally, the present study is the first study using hydroxyapatite for the treatment of non-union long-bone fractures, and showed convincing results as compared to autologous bone grafts. Further studies to substantiate and validate the findings of present study are also recommended.

Conclusion

Thus findings of present study showed that synthetic bone graft was well-accepted, had fewer complications and a higher bone-union rate among patients with non-union long-bone fractures. The present study is one of the basic studies showing use of hydroxyapatite as the synthetic bone graft for treatment of non-union long-bone fractures. Further studies are recommended to validate the reliability and validity of these results.

However more such studies are recommended to yield more authenticating results in terms of use of hydroxyapatile as substitute to autologous bone grafts for non-union of fractures.

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