The Clinical Use of NovaBone as Substitute Bone Graft for the Repair of Bone Defects

Abstract

Due to complications associated with autogenous bone harvesting, synthetic graft materials have been developed for osseous defect repairs associated with fractures or joint arthroplasty. One material, bioactive glass, has been demonstrated to stimulate bone formation in research studies. A one-year study in 29 patients evaluated the bioactive glass NovaBone in acute long bone fractures and revision procedures following delayed or non-unions. No complications were recorded. Continuous callus formation, bridging the defects, was observed at six months in 19 cases (65.5%) and in all patients (100%) by 12 months. The results in non-unions were comparable to literature reports for demineralized bone. At one-year, NovaBone was clinically effective for the repair of these osseous defects, reducing the need to harvest large amounts of autogenous bone.

Key Words: Non-unions, graft material, bioactive glass, Bioglass

Running Title: NovaBone as a Substitute Bone Graft

INTRODUCTION

In orthopaedics, the rate of healing of osseous defects is not uniform between individuals, varying with location, vascular sufficiency, patient age, and multiple other factors. To increase the incidence of healing, autogenous and allogenic bone are often used as graft materials. These tissues act as a physical scaffold for new bone growth, while also containing proteins that may act to increase local cell populations and accelerate healing.

Although generally effective in graft applications, tissue-based materials are often limited in availability. Autografts, the "gold standard" for bone grafting, often require a second surgical procedure if sufficient bone tissue is not available at the defect site. This is particularly true in revision arthroplasty cases where a loss of tissue is often associated either with the failure of the original implant or with the revision process itself. For orthopedic applications, harvest sites may include the iliac crest, the anterior tibia, segmental grafts from the fibula, and the ribs[1]. However, the use of these secondary sites also poses increased risk to the patient. The most common site for autograft harvest, the iliac crest, has been associated with numerous complications, ranging from infection and chronic pain to deformity and site fracture[2,3,4]. To reduce these complications, various synthetic materials have been developed for use in bone graft procedures.

One group of synthetic materials often used for different orthopedic repair processes are termed bioceramics[5]. These materials range in application from nearly inert materials for load-bearing applications (dense alumina and zirconia) to materials such as calcium sulfate, which may be used as a space filler and is rapidly absorbed from the graft site within a matter of weeks.

Another subgroup of bioceramics are the bioactive materials based on the calcium phosphorus system, which actually bond to local tissues[6]. These include calcium hydroxylapatite (HA) and tricalcium phosphate (TCP), both of which have been used as bulk and particulate materials to fill bone defects. These materials have a chemical composition similar to the mineral content of bone[7], with the TCP ceramics being absorbed over time while the HA ceramics are relatively insoluble. It is the apatite structure of HA that supports the direct attachment of new bone to the material surface[8].

Another series of calcium phosphate materials are the bioactive glasses and glass ceramics. In 1971, Hench reported that the bioactive glass Bioglass® was the first synthetic material that actually bonded to bone[9]. Bioglass® is a non-crystalline material produced from the oxides of calcium, phosphorus, sodium and silicon. Subsequent studies have demonstrated excellent biocompatibility, osteoconductivity and osteoproductivity, stimulating bone growth. When implanted into an osseous defect, a series of surface and bulk dissolution reactions occur to form a hydroxy-carbonate-apatite layer on the Bioglass® surface[10]. Local stem cells and collagen fibers are attracted and attach to the material surface. Cell differentiation and calcification of the attached tissues result in the formation of new bone around the particles. These reactions continue until the graft particles are ultimately absorbed, regenerating new bone in their place. This new tissue is bone, not a graft-bone composite as seen with non-absorbable grafts like HA[11,12.] While Bioglass products have been widely used in oral and maxillofacial surgeries as graft materials[13,14,15], there are few reports on the clinical use of Bioglass for the repair of orthopedic defects[16].

From 1998 to 1999, we studied NovaBone, a particulate Bioglass product, in a series of orthopaedic fracture patients. Subjects were grafted with NovaBone during either a revision procedure for a delayed or non-union, or as part of a primary procedure for compound fractures. The grafting in the primary treatments was performed as a prophylactic procedure to prevent possible non-unions. After one-year follow-up, we found that the material is clinically effective for the repair and healing of these defects.

MATERIALS AND METHODS

In this prospective study, clinical patients were implanted with the bioactive glass NovaBone® (USBiomaterials Corporation, Alachua, Florida USA). The material was implanted in grafting procedures either alone or mixed with autogenous or allogenic bone. NovaBone is a completely synthetic bone graft material, consisting of 45 % SiO_2, 24.5 % Na_2O, 24.5 % CaO, and 6% P_2O_5 by weight. It is supplied as a particulate with a size range of 90 - 710 µm.

Clinical Subjects

Clinical subjects requiring bone grafting for the repair of acute fractures or for revision of failed prior treatment were evaluated. A total of 29 consecutive cases presented for grafting were entered into the study, 20 male and 9 female, ranging in age from 19 to 58 years (average 32 years). The distribution of treatments is listed in Table I by site and indication. The revision surgeries for the eighteen delayed or non-unions were required as the result either of movement or breakage of the previous fixation (14 cases) or failure of conservative reduction and casting.

Table I. Summary of Clinical Cases by Indication and Location

Site	Open/Compound Fractures	Delayed Unions	Non-Unions	Total
Femur	3	2	--	5
Tibia	6	7	2	15
Humerus	2	4	3	9
Total Defects	11	13	5	29

Procedure

On exposure, the defect sites were debrided to remove necrotic tissues and expose bleeding bone. For cases of delayed or non-union, the scar/callus tissue around the fracture site was removed and several holes were drilled through the cortex into the marrow cavity to promote bleeding. Internal or external fixation was used in all cases to insure stabilization in all planes, and the defect sites were grafted with NovaBone. The NovaBone was prepared by mixing it either with the patient's blood from the defect site or with sterile saline to form a paste. In several cases, the NovaBone paste was mixed in a 1:1 ratio with autogenous bone. The prepared graft material then was placed into the site, filling all the voids around the fractured bone ends, and the defect site was closed. All grafting procedures were performed by the senior author.

Immediately following surgery, the patients were monitored for signs of clinical problems. The patients were recalled at periods of one, two, three, six and twelve months. Radiographs were taken and the site healing was examined. Clinical outcome was measured as a function of callus formation, with success being the formation of a continuous callus bridging the defect site. A five-point qualitative evaluation of callus formation was conducted, rating the extent of callus bridging from 1 - no callus formation to 5 - complete bridging of the defect.

RESULTS

No complications were recorded for any patient and no re-operations were necessary.

Postoperative recovery was uneventful with no side effects observed. Blood alkaline phosphatase levels were slightly elevated after surgery, but all remaining bloodwork was normal. No subjects were dropped from the study, with all subjects returning at the subsequent recall periods. Table II lists the clinical data for each patient, including subject demographics, graft site, indication, and qualitative healing status at the selected periods.

All radiographs were analyzed by the senior author. At six months, significant callus formation was observed in all cases, with 19 cases showing continuous callus formation and absence of the local fracture line, for a clinical healing rate of 65.5%. At 12 months, the clinical healing rate was 100%, with all defects showing continuous callus bridging of the former fracture site.

Analyzing the results by indication (Table III), nine of the eleven open/compound acute fractures were healed by six months. The remaining two patients healed by twelve months, for healing rates of 82% and 100% at six and twelve months, respectively. For the revision cases, ten of the eighteen patients were healed at six months (56%) with all patients being healed at 12 months.

Note that none of the subjects initially presenting for non-union showed evidence of callus formation at one month and were slower to heal than the other groups. However, by 12 months, as indicated in Table II, all non-unions were healed.

Table II. Subject Clinical Information and Results

Subject	Age	Sex	Site	Indication	Duration	Reason	Results - Callus Formation Rating*				
							1 m	2 m	3 m	6 m	12 m
1	33	M	Femur	Compound Fracture	Acute	Motor vehicle accident	1	3	3	5	5
2	20	F	Tibia	Compound Fracture	Acute	Motor vehicle accident	3	5	5	5	5
3	58	M	Tibia	Compound Fracture	9 days	Motor vehicle accident	1	1	2	4	5
4	25	M	Humerus	Compound Fracture	Acute	Fall	3	4	5	5	5
5	28	F	Tibia	Compound Fracture	4 days	Motor vehicle accident	2	2	4	5	5
6	38	M	Femur	Compound Fracture	Acute	Motor vehicle accident	2	4	5	5	5
7	20	M	Tibia	Compound Fracture	Acute	Fall	3	4	4	4	5
8	52	M	Tibia	Compound Fracture	6 days	Motor vehicle accident	1	1	2	5	5
9	36	F	Tibia	Compound Fracture	Acute	Motor vehicle accident	1	3	4	5	5
10	35	M	Humerus	Compound Fracture	18 days	Motor vehicle accident	1	2	3	5	5
11	28	M	Femur	Compound Fracture	Acute	Motor vehicle accident	3	3	4	5	5
12	31	M	Femur	Delayed Union	8 months	Failure of previous fixation	2	3	5	5	5
13	36	F	Tibia	Delayed Union	9 months	Failure of previous fixation	1	1	3	5	5
14	30	M	Tibia	Non-Union	11 months	Failure of previous fixation	1	1	1	3	5
15	24	M	Tibia	Delayed Union	6 months	Failed conservative treatment	3	5	5	5	5
16	40	M	Humerus	Non-Union	10 months	Failure of previous fixation	1	1	1	3	5
17	42	F	Tibia	Delayed Union	4 months	Failed conservative treatment	2	3	4	5	5
18	44	M	Tibia	Delayed Union	6 months	Failure of previous fixation	1	2	2	4	5
19	32	F	Tibia	Delayed Union	5 months	Failed conservative treatment	2	3	4	5	5
20	28	M	Femur	Delayed Union	7 months	Failure of previous fixation	2	3	5	5	5
21	56	M	Tibia	Non-Union	9 months	Failure of previous fixation	1	2	2	4	5
22	30	F	Tibia	Delayed Union	4 months	Failed conservative treatment	2	4	4	5	5
23	42	M	Humerus	Non-Union	9 months	Failure of previous fixation	1	1	2	4	5
24	33	M	Tibia	Delayed Union	5 months	Failure of previous fixation	2	2	4	5	5
25	56	F	Humerus	Non-Union	8 months	Failure of previous fixation	1	1	3	4	5
26	19	M	Humerus	Delayed Union	6 months	Failure of previous fixation	1	2	3	4	5
27	32	M	Humerus	Delayed Union	4 months	Failure of previous fixation	2	2	4	5	5
28	37	F	Humerus	Delayed Union	5 months	Failure of previous fixation	2	2	3	5	5
29	40	M	Humerus	Delayed Union	7 months	Failure of previous fixation	2	2	3	4	5

* Callus Rating Scale: 1 - not significant; 2 - small amount; 3 - medium amount; 4 - large amount; 5 – continuous

Table III. Site Healing Evaluation by Indication

Indication	Callus Rating* by Time														
	1 month					3 months					6 months				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Acute Fracture (n=11)	5	2	4	-	-	-	2	2	4	3	-	-	-	2	9
Delayed Union (n=13)	3	9	1	-	-	-	1	4	5	3	-	-	-	3	10
Non-union (n=5)	5	-	-	-	-	2	2	1	-	-	-	-	2	3	-

* Callus Rating Scale: 1 - not significant; 2 - small amount; 3 - medium amount; 4 - large amount; 5 – continuous

Case Studies

Case Study I (Subject #17)

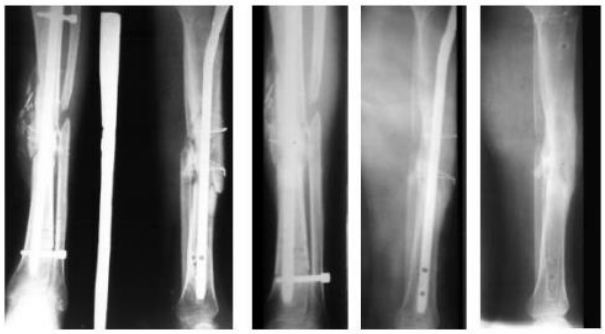
A 42-year-old male with a four-month delayed union of tibia/fibula fractures resulting from an automobile accident. The patient returned to the clinic after failure of original conservative treatment consisting of application of a plaster cast (Figure 1). The defect was debrided and an intramedullary rod placed in the tibia. The tibial defect site was grafted with 10cc of NovaBone mixed with blood. Remodeling of the early callus was observed at three months, with continuous bridging of the defect observed by six months. The internal fixation removed at twelve months.

Case Study 2 (Subject #20)

A 28-year-old male presented with a delayed union of the femur of seven-month duration. The original fracture was fixed with a compression bone plate, which subsequently fractured, as observed on pre-operative radiographs (Figure 2). At re-entry, the original plate and screws were removed and an intramedullary rod placed to stabilize the defect. The site was grafted with NovaBone mixed with the patient's blood. Partial medial bridging of the defect site was seen at three months, with additional consolidation at four months, although there was some medial cortical degeneration. At twelve months, a mature lateral callus has formed and the intramedullary rod was removed. Solid fusion at the fracture site was observed at 14 months.

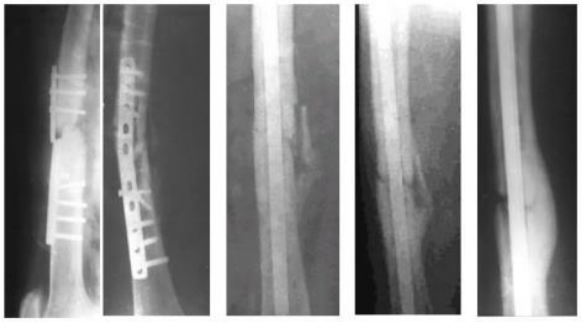
Case Study 3 (Patient #10)

A 35-year-old male was treated for a spiral fracture of the humerus 18 days after involvement in a motor vehicle accident. Open reduction of the fracture was performed, followed by grafting of the site with 10 cc of NovaBone and placement of an external fixator. By six months, the fracture is healed and the external fixator and screws have been removed.



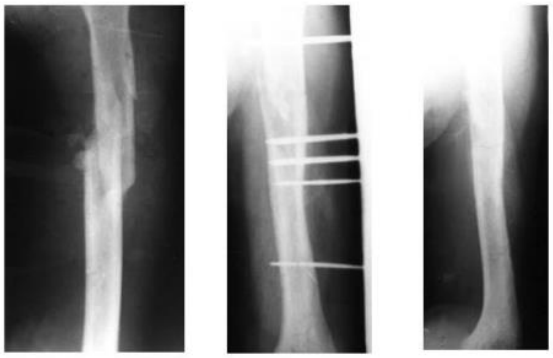
A) B) C) D)

Fig 1. Radiographs of tibia/fibula non-union four months after conservative treatment failure. Intramedullary rod stabilization with NovaBone grafting of tibia. A: Immediate post-operative, B: 3 months pos-operative, C: 6 months post-operative, D: 12 months post-operative. Solid fusion of the tibia was observed with removal of the internal fixation



A) B) C) D)

Fig 2. Radiographs of delayed union resulting from failed compression plating of femoral fracture. Plate removed and intramedullary rod placed with NovaBone grafting. A: Pre-operative, B: 3 months post-operative, C: 4 months post-operative, D: 12 months post-operative. Large lateral callus bridging the defect site, with some medial cortical absorption.



A) B) C)

Fig 3. Acute spiral fracture of the humerus following motor vehicle accident. NovaBone grafting of humerus with external fixator placed. A: Pre-operative, B: 1 month post-operative, C: 6 months post-operative. Stable fusion was obtained at six months, with removal of external fixator.

LEGENDS TO FIGURES

Fig 1. Radiographs of tibia/fibula non-union four months after conservative treatment failure. Intramedullary rod stabilization with NovaBone grafting of tibia. A: Immediate post-operative, B: 3 months pos-operative, C: 6 months post-operative, D: 12 months post-operative. Solid fusion of the tibia was observed with removal of the internal fixation.

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DISCUSSION

Fracture healing occurs via a complex combination of physiologic processes to restore the bone mechanical integrity. Fracture repair is divided into two modes, primary and secondary. Primary healing occurs when the ends of the bone are suitably aligned and stabilized so that direct cortical repair occurs across the gap. More typical, however, is secondary healing, defined by the formation of a callus that bridges the fracture site to stabilize the bone ends. Typically, the callus is formed during the first two weeks following injury, initiated by cells recruited from the periosteum and/or endosteum. Cells differentiate or migrate to the injury site, resulting in the regional proliferation of osteoblasts and chondrocytes. Intramembranous ossification and endochondral bone formation produce the bulk of the callus, which subsequently remodels to result in solid bone union.

In some cases, however, bone healing is disrupted before completion, resulting in a delayed or non-union. Predicting whether a specific fracture will result in a delayed union is difficult due to the wide range of potential causes. Various local or systemic conditions play a role in reducing the healing response, ranging from local infection and extent of tissue damage to malnutrition and diabetes[17]. The size of the fracture gap also is cited as a source of union failures[18].

To reduce the possibility of impaired fracture healing, autogenous or allogenic bone often is used as a graft. These tissues act as a physical scaffold for new bone growth while also containing proteins that may act as chemotactic or morphogenic agents to increase local cell populations and accelerate healing. In one study using allograft, a series of 48 non-unions and delayed unions were repaired using a combination of bone plate internal fixation and demineralized bone matrix (DBM)[19]. At six months, the healing rate was 60%, reaching 89% at twelve months.

In this study, patients were treated with NovaBone synthetic bone graft material. During the revision procedures, the prior scar or callus tissue was removed and holes were drilled through the cortex into the marrow cavity. Drilling these holes served to stimulate the production of bone morphogenic proteins (BMP) by the local tissues[20], the BMPs playing an important role in the repair and reconstruction of bone defects. In addition, blood passing up through these holes into the NovaBone material supplied osteoprogenitor cells and growth factors to the defect site. These growth factors and cells attach to the particle surfaces to ultimately form new bone. In this study, this bone formation was observed on the radiographs as new callus formation and maturation.

The subjects were grafted during either a revision procedure after a delayed or non-union, or during a primary procedure for compound or open fractures to encourage healing and prevent possible non-unions. NovaBone application during the primary procedure resulted in 6-month and 12-month healing rates of 82% and 100%, respectively. For delayed unions or non-unions, NovaBone was used to stimulate healing in previously impaired cases. The 6-month and 12-month healing rates were 56% and 100%, which compare favorably to the 60% and 89% healing rates reported above for DBM.

Many factors may be responsible for the clinical impairment of fracture healing, which may result in delayed union or non-unions. In this study, we evaluated the synthetic bone graft material NovaBone for the repair or prevention of delayed unions and non-unions in 29 patients. Healing rates in this study were comparable to those reported in the literature for demineralized bone matrix. Use of this synthetic graft material reduces the need for harvesting large amounts of autogenous bone and the complications often associated with graft harvest. After one-year follow-up, we found that NovaBone is clinically effective for the repair of these defects, with a clinical fusion rate of 100% at 12 months.

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