Clinical Performance of *NeuGraft*® in the Management of Fractures and Osseous Defects in the Appendicular Skeleton

A review of *Collagraft* (NeuGraft)* Multicenter Clinical Trials 297 subjects and 345 fractures/88 subjects and 102 fractures

Background and Significance

Because of extensive comminution or loss of bone, the effective surgical management of many long bone fractures and defects often requires that bone graft be implanted at the defect site to facilitate adequate healing and to ensure satisfactory postoperative outcomes. Bone harvested from the patient's own ilium (i.e., autologous bone or autograft) is used in many of these procedures. Iliac crest autograft is the preferred graft material among orthopedic surgeons because of its inherent immunologic- and histo-compatibility and because it furnishes an immediate source of osteoprogenitor cells at the site of implantation to promote new bone formation and timely graft incorporation (29). However, autologous bone can be of limited supply especially among older osteoporotic individuals and pediatric patients as well as in patients where multiple operative procedures are anticipated over time (29). It has been estimated that an iliac crest donor site requires approximately 24 months to regenerate before it could be reutilized to supply adequate tissue for further autotransplantation (2).

More importantly, there has been a growing understanding of the frequency and severity of morbidity associated with harvesting autologous bone from a second operative site, such as the iliac crest (3). Russell and Block (4) estimated that the incidence of major complications associated with bone graft harvesting ranged from 2.5% to 39%. These serious adverse events produce incapacitation, significant disability, or impairment of function and/or quality of life and usually necessitate operative, pharmacologic and/or rehabilitative intervention. Chronic and severely bothersome pain at the donor site is the most common serious complaint reported by patients who have undergone bone graft harvesting (5). Other complications include neurologic and vascular injuries, deep infections, hematoma, as well as instability and fracture of the pelvic bony structure and abdominal herniation (4).

Allogeneic demineralized bone matrix processed from human cadaver bone also is a readily available graft material. However, there is always some potential for disease transmission when using allograft, and this material is only mildly osteoinductive (6) and probably requires the addition of autologous bone marrow to assure satisfactory outcomes in challenging grafting procedures (7). Moreover, the inductive potential of demineralized bone has been shown to vary widely depending on a number of factors including the methods used to process the material by different tissue banks (8, 9) and the age of the donor (10-12).

A number of ceramic analogs of bone, such as hydroxyapatite and tricalcium phosphate, have shown promise as alternative graft materials because they have exceptionally good tissue compatibility and because they bond directly to native bone without an intermediary layer of connective tissue (13-15). These materials are essentially osteoconductive matrices, acting as substrates that provide a favorable scaffolding for vascular ingress, cellular infiltration and attachment, cartilage formation, and calcified tissue deposition (15-17). Nonetheless, the clinical success of many challenging orthopedic reconstructive procedures requires that the bone graft material also supply an osteogenic stimulus at the defect site to promote new bone formation. In these cases, calcium phosphate grafting materials are normally contraindicated when used alone because they do not encourage timely or consistent healing compared to autograft (18). However, the addition of autologous bone marrow to various ceramic biomaterials provides a composite graft that has both osteoconductive and osteoinductive characteristics (19-23). Use of these composite grafts eliminates the need to harvest autologous bone from a second operative site.

This report summarizes the results of two large multi-center trials where *NeuGraft/Collagraft* Bone Graft Matrix was evaluated for the treatment of long bone fractures. The first trial involved the use of *Collagraft* Paste compared to iliac crest autograft using a randomized study design, and the subsequent trial, used a second generation product: *NeuGraft/Collagraft* Strip.

*NeuGraft Strip and Collagraft Bone Graft Matrix Strip (Collagraft Strip) are the same products. They have identical chemical composition and indications for use, but use different trade names and are sold through different channels of distribution. Both products are manufactured by NeuColl, Inc. www.neucoll.com

Patients, Methods and Outcomes

The first clinical trial involved 18 geographically-dispersed U.S. medical centers participating in a randomized controlled trial to determine the safety and effectiveness of *Collagraft* Paste compared to autologous bone in the treatment of traumatic fractures and osseous defects in the femur, tibia, humerus, radius and ulna. Subjects were assigned randomly to fracture treatment with either *Collagraft* Paste or autograft. Randomization was stratified within each clinical center and separately for weight bearing and non-weight bearing sites. *Collagraft* Paste is a composite graft consisting of equal mass proportions of a bovine fibrillar collagen suspension and a biphasic [hydroxyapatite (65%) and tricalcium phosphate (35%)] granular ceramic. This composite is mixed intraoperatively with autologous bone marrow aspirated from the ilium in a volume ratio of four parts *Collagraft* Paste to one part marrow. The graft material used in this study had a paste-like consistency. Subjects assigned to treatment with autograft had cancellous bone graft harvested from the posterior iliac crest.

A total of 297 subjects (345 fractures) qualified for inclusion and were treated with either *Collagraft* Paste and autologous bone marrow (176 fractures) or iliac crest autograft (169 fractures). The findings of this investigation have been reported previously (24-26) with the most recent report (26) summarizing the results of subjects with an average 24 months of postoperative follow-up.

Following completion of the randomized controlled trial, a separate group of subjects was treated with *NeuGraft/Collagraft* Strip. The Strip form of *NeuGraft/Collagraft* Bone Graft Matrix is identical to the paste material except that it is lyophilized at the timeof processing. *NeuGraft/Collagraft* Strip was coated intraoperatively with autologous bone marrow in a 4:1 volume ratio after rehydration in sterile saline. No control subjects were included in this second study. This trial involved 88 subjects (102 fractures) with identical inclusion and exclusion criteria recruited from six clinical sites. Twelve month clinical and radiographic follow-up data were available for 83 of these fractures and were evaluated to confirm the safety and effectiveness of *NeuGraft/Collagraft* Strip compared to *Collagraft* Paste for treating long bone fractures.

Subjects in both studies were monitored at 1.5, 3, 6, 12, 18 and 24 month intervals. Fracture healing was judged at each clinical site separately as well as by a blinded independent skeletal radiologist. Union of the fracture was defined as the first radiographic evidence of healing using precise criteria regarding callus formation, graft site appearance, and proximal and distal healing (26). Only the fracture healing results provided by the independent radiologist are provided herein (Table 2). Evaluations were made of wound healing, fracture site and autograft bone or bone marrow aspirate site pain severity, impairment of physical function, and adverse events.

Clinical Findings

Baseline characteristics and surgical details for the two treatment groups participating in the randomized trial as well as for the separate group of subjects treated in the subsequent trial with the *NeuGraft/Collagraft* Strip are provided in Table 1. There were no clinically relevant or statistically significant differences between treatment groups in the randomized trial for most baseline factors with the exception of operative duration which was approximately 15% longer among subjects treated with autograft (153 versus 133 minutes, respectively; p=0.053).

The rates of bony healing were strikingly similar between treatment groups at each postoperative interval (Table 2). By 12 months postoperatively, 90% of autograft treated subjects and 86% of *Collagraft* Paste treated subjects were considered healed. In the *NeuGraft/Collagraft* Strip trial, the 12 month healing rate was approximately 92% which was equivalent to the healing rates achieved with *Collagraft* Paste and iliac crest autograft (Table 2). The median time to healing for subjects treated with *NeuGraft/Collagraft* Strip and *Collagraft* Paste was 24.0 weeks and 33.6 weeks, respectively (p>0.10).

Operative site healing was uneventful among all subjects in both studies, with greater than 90% of individuals showing complete wound healing within three months of surgery. Importantly, the rate of fracture site infections was significantly lower in the *Collagraft* Paste group (5%) compared to the autograft control group (13%) (p=0.008). There were 6 revision surgeries for failed fracture healing in the *Collagraft* Paste group and 15 revision surgeries among subjects treated with autograft. Additionally, 31% of autograft subjects complained of donor site pain in the hip at 6 weeks postoperatively, with 5% reporting chronic donor site pain after 24 months. By comparison, none of the subjects treated with either *Collagraft* Paste or *NeuGraft/Collagraft* Strip reported any donor site pain in the hip at any time. When compared independently to the overall complication rate among autograft subjects, a lower overall rate was realized with the Strip form of *NeuGraft/Collagraft* Bone Graft Matrix including a significantly lower rate of infections.

Discussion and Significance

Osteoconductive matrices support the ingress of bone into the grafted bone defect (14, 15). However in challenging surgical applications where large segments of bone require repair (e.g., comminuted fractures), a purely osteoconductive graft is unlikely to provide satisfactory performance. Several studies suggest that the graft performance of ceramic-based graft materials is enhanced by the addition of autologous bone marrow, a source of viable osteoprogenitor cells (6, 21, 23, 27). Indeed, the multicenter, randomized controlled trial of *Collagraft* Paste summarized herein, as well as the separate study of subjects treated with the *NeuGraft/Collagraft* Strip, utilized aspirated autologous marrow as an integral component of the graft with excellent results (26).

Composite grafting materials combining ceramic analogs of bone and autologous bone or marrow have been used previously to bridge critical sized defects in animal models (20, 28). By extension, the *NeuGraft/Collagraft* composite material used in the current studies combines organic (i.e., collagen) and inorganic (i.e., hydroxyapatite/tricalcium phosphate) matrices that mimic closely the constituents of native bone. The addition of autologous marrow to this composite at the time of surgery supplies important bone forming cells to the graft site. The healing response to *NeuGraft/Collagraft* Bone Graft Matrix as observed radiographically exhibited a pattern of callus remodeling and graft incorporation quite similar to that observed with autologous bone. Indeed, inspection of the healing rates demonstrates a striking similarity across all three treatment groups irrespective of postoperative follow-up (Table 2). This finding is particularly impressive in light of the fact that the independent radiographic reviewer was blinded to treatment assignment (randomized trial only), follow-up interval and subject's medical disposition.

In addition, the subjects treated with *NeuGraft/Collagraft* Strip achieved a similar fracture healing pattern as compared to both treatment groups in the randomized trial (Table 2). The 12 month rates of solid healing were similar across the three study groups (i.e., 86%, 90%, and 92%, respectively for patients treated with *Collagraft* Paste, autograft, and *NeuGraft/Collagraft* Strip) (Table 2). Because the *NeuGraft/Collagraft* Strip treated subjects had the same baseline characteristics as the subjects participating in the randomized trial, it was concluded that this second generation form of *Collagraft* Bone Graft Matrix, *NeuGraft/Collagraft* Strip offers equivalent performance in the clinical setting. Additionally, the solid, porous, but pliable consistency of *NeuGraft/Collagraft* Strip provides improved storage and surgical handling characteristics. These two large multi-center clinical trials with long-term follow-up demonstrated that *Collagraft* Paste, *NeuGraft/Collagraft Strip* and autologous bone are equivalent with respect to long bone fracture healing, clinical outcomes and postoperative complications.

Table 1: Selected Background Characteristics and Surgical Details by Treatment Group**

	***Collagraft* Paste**	**Autograft**	***NeuGraft/Collagraft* Strip**
Mean Age (years)	37.0	36.5	36.0
Gender			
Male	70.0%	68.0%	69.9%
Female	30.0%	32.0%	30.1%
Fracture Type [%, (freq.)]			
Open	31.3% (55/176)	27.8% (47/169)	13.7% (14/102)
Closed	68.7% (121/176)	72.2% (121/169)	86.3% (88/102)
Anatomic Location [%, (freq.)]			
Tibia	36.9% (65/176)	36.1% (61/169)	37.3% (38/102)
Femur	21.0% (37/176)	20.7% (35/169)	10.8% (11/102)
Humerus	5.1% (9/176)	10.0% (17/169)	21.6% (22/102)
Radius	17.0% (30/176)	17.8% (30/169)	11.8% (12/102)
Ulna	20.0% (35/176)	15.4% (26/169)	18.6% (19/102)
Fracture Location [%, (freq.)]			
Diaphyseal	55.7% (98/176)	61.0% (103/169)	56.9% (58/102)
Metaphyseal	41.5% (73/176)	34.3% (58/169)	37.3% (38/102)
Not Classified	2.8% (5/176)	4.7% (8/169)	5.9% (6/102)
Comminuted Fracture [%, (freq.)]	73.9% (130/176)	72.2% (122/169)	70.6% (72/102)
Instrumentation [%, (freq.)]			
Internal Fixation	89.8% (158/176)	92.9% (157/169)	94.1% (96/102)
External Fixation	10.2% (18/176)	7.1% (12/169)	5.9% (6/102)
Operative Duration (minutes)	133	153	178

* Descriptive statistics provided for number of subjects and fracture characteristics provided for number of fractures.

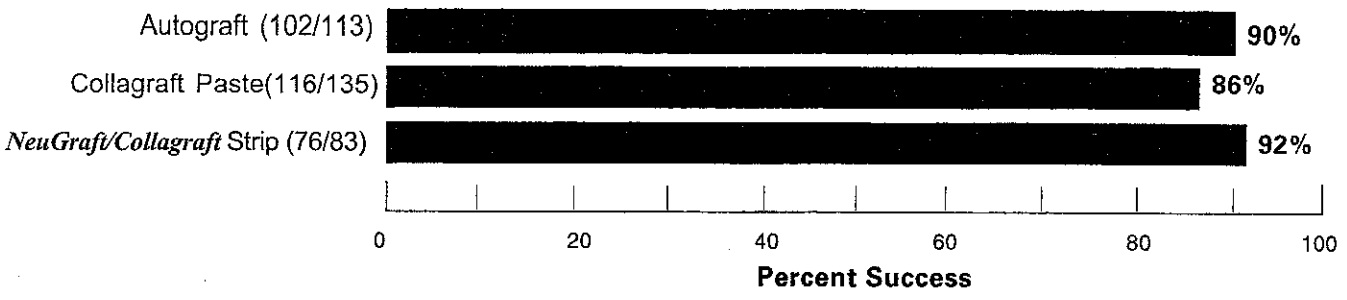
Table 2: Healing Rates by Treatment Group*

Post Operative Intervals (mos.)	*Collagraft* Paste	Autograft	*NeuGraft/Collagraft* Strip
3	27.7%	30.9%	52.4%
6	59.0%	68.5%	75.9%
12	86.0%	90.3%	91.6%

** Evaluation provided by an independent radiographic reviewer.

† Frequency and percentage distributions presented for the number of fractures evaluated at each postoperative interval.

Success Rate (at 12 months) *Expressed as a percentge of the patients evaluated both clinically and radiographically.*



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