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Revisional Hindfoot and Ankle Arthrodesis Using Recombinant Human Platelet-Derived Growth Factor and Beta-Tricalcium Phosphate

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Abstract

Background: The overall incidence of nonunion following primary arthrodesis in foot and ankle surgery is approximately 11%, with higher rates expected for revisional arthrodesis. Use of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) combined with beta-tricalcium phosphate (β-TCP) in primary hindfoot and ankle arthrodesis results in comparable fusion rates, less pain, and fewer side effects compared to autograft. This study evaluated the use of rhPDGF-BB/β-TCP in revisional arthrodesis in hindfoot and ankle reconstruction surgery.

Methods: The charts of patients with at least 12 months follow-up who had undergone revisional arthrodesis supplemented with rhPDGF-BB/β-TCP of the talonavicular, calcaneocuboid, subtalar, or ankle joints were retrospectively reviewed. Comorbidities included Charcot neuroarthropathy (42%), neuropathy (33%), diabetes (33%), hypertension (33%) and gastroesophageal reflux disease (8%).

Results: Twelve patients were included, of which 11 (91.7%) achieved union. The mean time to fusion was 12.9±1.9 weeks and to return to activity was 16.6±2.8 weeks. One patient developed a nonunion of the talonavicular joint. No complications related to the grafting material were observed. There were 2 infected hematomas, both of which went on to fusion.

Conclusion: Use of rhPDGF-BB/β-TCP is a viable alternative to autograft for revisional rearfoot arthrodesis, even in high-risk patients, without the pain and morbidity associated with autograft harvesting.

Keywords: Ankle; Arthrodesis; Fusion; Hindfoot; Nonunion; Revision; rhPDGF-BB

Introduction

Nonunion is a major complication following foot and ankle arthrodesis and places a great burden on the patient and surgeon. The consequences of nonunion include continued pain, poor patient satisfaction, the possibility of chronic disability, and an increased healthcare cost. The overall incidence of nonunion following primary arthrodesis of the foot or ankle is reported as 10% to 11%, but this rate is substantially higher in patients with risk factors such as smoking, diabetes, and obesity [1-4]. Rates of nonunion following a revision arthrodesis are higher than for primary arthrodesis. O'Connor et al. reported 19 (23%) cases of nonunion in 82 patients who underwent a revision procedure for nonunion of hindfoot or midfoot arthrodesis [5]. In a study of 184 isolated subtalar fusions, Easley et al. reported 8 (29%) nonunions in a subset of 28 patients undergoing revision, compared to 22 (14%) nonunions after 156 primary arthrodesis [6].

Autogenous bone graft (autograft) [6-8], allograft [9-11], and, more recently, orthobiologic alternatives have been used extensively to promote bony fusion in patients considered at higher risk for nonunion, with few high-level studies to support this practice. In a recent level II study, the presence of more than 50% of graft material in the fusion space in hindfoot and ankle arthrodesis in 573 joints demonstrated significantly higher fusion rates at 24 weeks [12].

Autogenous bone graft is ideal for high-risk arthrodesis, but can cause substantial morbidity. The harvesting of autograft for use in promoting joint fusion has well-documented complications at the autograft donor site, including chronic pain, blood loss, fracture, seroma, scarring, infection, heterotopic ossification, and hernia [13-16]. Furthermore, harvesting of autograft requires additional operative time and/or personnel, which incurs additional costs [14,17,18]. While allograft circumvents some of the complications associated with autograft, its use has otherrisks, such as disease transmission, variable preservation practices, potential structural weakness, and a possible increased risk of non-union [9,10]. Recombinant human platelet-derived growth factor-BB (rhPDGF-BB), the most active isoform of platelet-derived growth factor in bone and other connective tissues, has been used successfully to promote fusion in primary hindfoot and ankle arthrodesis. In a large, multicenter, randomized, non-inferiority clinical trial of 434 patients who underwent primary arthrodesis of 597 hindfoot and ankle joints, treatment with rhPDGF-BB combined with a beta-tricalcium phosphate (β-TCP) osteoconductive scaffold resulted in comparable fusion rates, less pain, and fewer side effects compared to treatment with autograft [19]. A second multicenter, randomized clinical trial that utilized rhPDGF-BB combined with an injectable, osteoconductive β-TCP-collagen matrix in primary hindfoot and ankle fusions also reported equivalent fusion rates, clinical success, and safety-related outcomes to autograft, while eliminating the pain and morbidity associated with autograft harvesting [20].

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The purpose of this study was to assess the safety and effectiveness of rhPDGF-BB/β-TCP as a bone graft substitute for revisional arthrodesis in hindfoot and ankle reconstruction surgery. Our hypothesis was that fusion rates for rhPDGF-BB/β-TCP will compare favorably to historical controls when used in revisional rearfoot arthrodesis, and without the complications associated with the use of autograft.

Patients and Methods

Study design

In this retrospective case series, the charts of all patients at two institutions who had undergone revisional surgery of a primary arthrodesis at the talonavicular, calcaneocuboid, subtalar, or ankle joints, between September 2015 and September 2017, and who had a minimum follow-up of 12 months were reviewed. Only patients who received supplemental graft material, specifically a combination of rhPDGF-BB (0.3 mg/mL) and β-TCP (Augment Bone Graft; BioMimetic Therapeutics Inc., now Wright Medical Technologies, Franklin, TN) during the revision surgery were included. Cases were excluded if they utilized more than 9 cc of graft material, had a history of infection at the surgical site prior to the revision surgery, and had less than 12 months of follow-up. This study was approved by both institutions' research ethics committees. Patients provided written, informed consent at the time of surgery that their data may be used for research purposes.

Patients were treated with ankle or hindfoot fusions using standard internal fixation and/or external fixation techniques. The individual components of the graft material (rhPDGF-BB liquid and β-TCP matrix) were mixed and allowed to sit for at least 10 minutes to maximize saturation prior to insertion at the fusion site. A regional block using 0.5% bupivacaine and 1% lidocaine was administered perioperatively, and standard postoperative analgesia was directed by the surgeon as necessary for pain management.

Postoperative clinical evaluations were conducted at 1, 3, 5, 7, 9, and 12 weeks postoperative, with radiographs taken at each visit. Computed tomography (CT) scans were obtained an average of 14 weeks postoperatively. Patients progressed to weightbearing upon assessment of radiographs and CT scans for fusion at the operative sites. Patients were continued to be followed in the office for at least 12 months for further clinical evaluation.

Patients

Twelve feet in 12 patients (7 males; 5 females) underwent revisional rearfoot or ankle arthrodesis using rhPDGF-BB/β-TCP (Table 1). The mean age at time of revision surgery was 56.9 ± 13.2 years (range: 33 to 75 years). The mean body mass index (BMI) was 34.9 ± 7.4 (range: 25.1 to 38.8); four (25%) patients were overweight, and eight (75%) patients were obese. Comorbidities included Charcot neuroarthropathy (5/12, 42%), neuropathy (4/12, 33%), diabetes (4/12, 33%), hypertension (4/12, 33%) and gastroesophageal reflux disease (1/12, 8%). Two patients (17%) were smokers (case #3 and #11). Three patients underwent ankle fusion, two of the subtalar joint (Figure 1), four underwent arthrodesis of the talonavicular joint (Figure 2), two of the subtalar, talonavicular and calcaneocuboid joints, and one of the subtalar and talonavicular joints (Table 2). One patient required external fixation with a bent wire technique (Figure 3). Patients were reviewed at a mean follow-up of 19.0 ± 8.2 months (Range: 11 to 35 months).

Study outcomes

The primary outcome for this study was the time to union, as assessed by the performing surgeon, based on CT scans, radiographs, and clinical examination. On radiographs, joint was considered fused if at least 50% osseous bridging at the fusion site was observed. On CT scans, a joint was considered fused if at least 50% osseous bridging across the articulation was observed. On clinical examination, the joint was considered fused if there was no movement at the site and no edema. Secondary outcomes included adverse events related to the graft material, and the time to return to activity, which was defined as weightbearing in a boot or shoe.

Case	Sex	Age at Surgery (years)	BMI (kg/m^2)	Comorbidities
1	Male	75	25.1	gastroesophageal reflux disease
2	Male	55	30.4	Charcot neuroarthropathy
3	Male	45	29.4	alcoholic neuropathy, Charcot neuroarthropathy
4	Female	52	28.3	None
5	Male	65	36.2	Charcot neuroarthropathy
6	Female	73	38.2	diabetes mellitus, Charcot neuroarthropathy, hypertension
7	Male	69	32.6	Charcot neuroarthropathy
8	Female	43	38.8	None
9	Female	50	54.1	diabetes mellitus, neuropathy, hypertension
10	Female	55	37.8	diabetes mellitus, neuropathy, hypertension
11	Male	33	33	None
12	Male	68	34.3	diabetes mellitus, neuropathy, hypertension
Mean ± SD		56.9 ± 13.2	34.9 ± 7.4	

Table 1: Patient demographics.

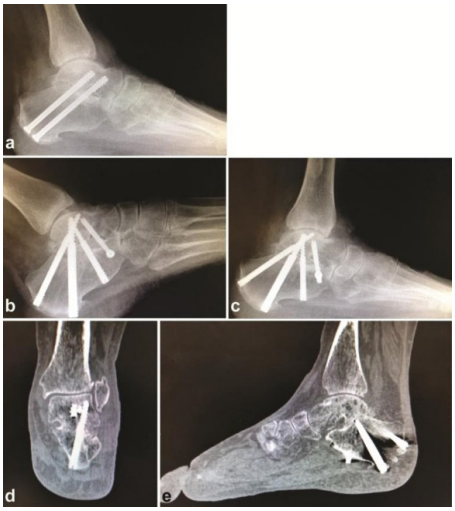

Figure 1: Case #9, a 50-year-old female with diabetes, neuropathy, and hypertension, who had previously undergone subtalar arthrodesis of the left foot. (A) Preoperative lateral radiograph indicates nonunion of the subtalar joint. The patient underwent revision subtalar joint fusion with new hardware and rhPDGF-BB/β-TCP. Postoperative radiographs at (B) 6 weeks and (C) 14 weeks, and (D, E) CT scans at 10 weeks demonstrate fusion of the subtalar joint.

Statistical analysis

Means and standard deviations were calculated for continuous variables. Categorical variables are reported as numbers and proportions.

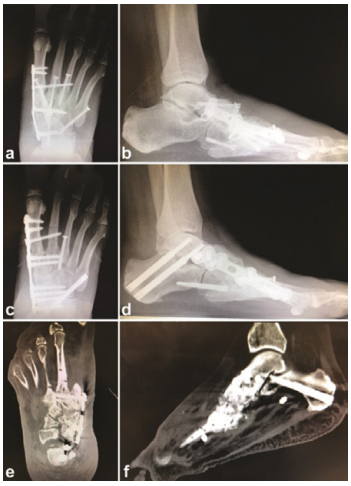

Figure 2: Case #5, a 65-year-old male who had undergone medial column fusion of the right foot for Charcot reconstruction two years earlier and presented with nonunion of the talonavicular joint. (A) Preoperative anteroposterior and (B) lateral radiographs. The patient required revision arthrodesis with new hardware and rhPDGF-BB/β-TCP. At 15 weeks postoperative, anteroposterior (C) and lateral (D) radiographs demonstrated joint fusion, which was confirmed by CT scans (E, F).

Case	Primary Surgery	Revision Site	rhPDGF-BB/β-TCP (ml)	Time to Union* (Weeks)	Return to activity (weeks)	Follow-up (Months)	Complications/Adverse events
1	Subtalar fusion	Subtalar	1.5	12	17	24	
2	Triple arthrodesis	Subtalar, Talonavicular, Calcaneocuboid	3	14	20	32	Infected hematoma; multiple incision and drainage, intravenous antibiotics
3	Ankle fusion	Ankle	3	14	17	12	-
4	Talonavicular fusion	Talonavicular	1.5	Nonunion	Nonunion	11	Nonunion
5	Medial column fusion	Talonavicular	3	12	16	35	-
6	Medial column fusion	Talonavicular	3	14	19	18	
7	Medial column fusion	Talonavicular	3	15	18	25	
8	Subtalar fusion and Medial column fusion	Subtalar, Talonavicular	3	14	15	13	Infected hematoma; resolved with oral antibiotics
9	Subtalar fusion	Subtalar	3	8	10	18	-
10	Triple arthrodesis x2	Subtalar, Talonavicular, Calcaneocuboid	3	14	20	12	
11	Malunion – ankle	Ankle	3	13	15	12	
12	Malunion – ankle	Ankle	3	12	16	16	
Mean ± Standard Deviation				12.9 ± 1.9	16.6 ± 2.8	19.0 ± 8.2	

*As determined by combination of radiological and clinical finding

Table 2: Individual Case Results Following Revision Arthrodesis of the Ankle or Hindfoot, using rhPDGF-BB/β-TCP.

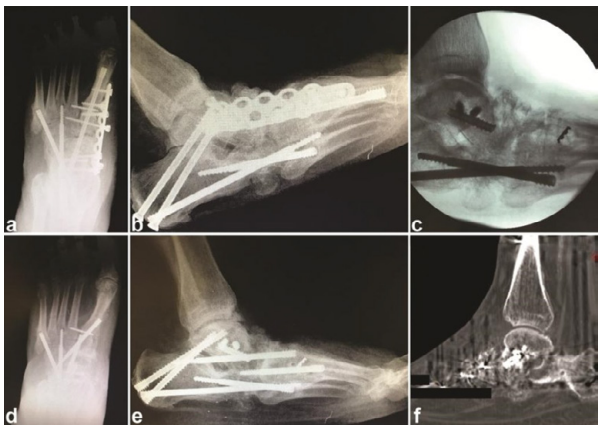

Figure 3: Case #7, a 69-year-old male who had previously undergone Charcot reconstruction developed a nonunion of the talonavicular joint with broken hardware, as observed in preoperative anteroposterior (A) and lateral (B) radiographs. The patient required removal of the broken hardware (C) and revision arthrodesis with rhPDGF-BB/β-TCP and application of external fixator with a bent wire technique. (D,E) Radiographs at 18 weeks postoperative demonstrate fusion. (F) At 15 weeks postoperative, CT scan confirmed fusion.

Results

Eleven of 12 patients (91.7%) demonstrated union, as defined by a combination of radiographic consolidation and clinical findings. The mean time to fusion was 12.9 ± 1.9 (range: 8 to 15) weeks (Table 2). The mean time to return to activity was 16.6 ± 2.8 (range: 10 to 20) weeks.

One patient developed a nonunion of the talonavicular joint and was scheduled for further surgical management. There were no adverse reactions or complications related to the grafting material. Two (16.7%) cases were complicated by an infected hematoma. One was resolved with oral antibiotics. The other case required multiple incision and drainages with intravenous antibiotics for resolution of the infection. Both cases went on to fusion.

Discussion

In this retrospective case series, 11/12 (91.7%) patients who underwent revisional arthrodesis of the ankle or hindfoot using rhPDGF-BB/β-TCP demonstrated union based on a combination of radiographic and clinical findings, with no adverse events or complications specifically related to the graft material.

These results are consistent with a previous report of rhPDGF-BB/β-TCP used in primary hindfoot and ankle arthrodesis. In that randomized, controlled, non-inferiority, clinical trial, 348/394 (88.3%) joints were considered clinically healed at 52 weeks following primary arthrodesis with rhPDGF-BB/β-TCP [19].

The 91.7% union rate observed in this study is also consistent with fusion rates reported for primary arthrodesis of hindfoot and ankle joints using autograft. In the same randomized clinical trial, 177/203 (87.2%) joints that underwent primary hindfoot or ankle arthrodesis with the use of autograft were considered clinically healed at 52 weeks [19]. Easley et al., reported 104/123 (84.6%) joints that underwent isolated subtalar arthrodesis using cancellous or structural autograft achieved clinical union at a mean of 51 months postoperatively [19]. In a logistic regression analysis of data from 159 studies of foot and ankle arthrodesis, the estimated probability of fusion was 94.2% in 1025 patients across 50 studies that utilized structural autograft and 93.7% in 2263 patients across 74 studies that utilized cancellous autograft [21].

All the patients in this study underwent revisional arthrodesis in rearfoot and ankle reconstruction surgery. The fusion rate following revision arthrodesis of the hindfoot or midfoot has been reported to be lower when compared to primary arthrodesis, ranging from 71% of 28 patients in study by Easley et al., to 77% in 82 patients who underwent revision arthrodesis in a study by O'Connor et al.[5,6]. In our series of 12 patients, only one patient did not achieve union, for an overall fusion rate of 91.7%.

Many of the patients in the current study presented with one or more comorbidities established to be risk factors for non-union [3,8]. Four patients presented with Charcot neuroarthropathy, three patients presented with diabetes mellitus, neuropathy, and hypertension, and one patient presented with diabetes mellitus, Charcot neuroarthropathy and hypertension. All these patients achieved union following revision arthrodesis with rhPDGF-BB/β-TCP. Interestingly, the only patient in our study who did not achieve fusion following revision arthrodesis had no medical comorbidities and did not smoke.

No complications associated with the graft material were observed in this study. In contrast, the harvesting of autograft is associated with numerous potential complications at the autograft donor site, including chronic pain, blood loss, fracture, seroma, scarring, infection, heterotopic ossification, and hernia [13-16]. While the use of allograft avoids some of these complications, other risks associated with allograft include disease transmission, variable preservation practices and potential structural weakness, and the risk of nonunion may be greater when using allograft [9,10,21].

Conclusion

Limitations of this study include the retrospective collection of data and the small sample size. A larger sample size would be required to permit statistical analyses, but that would require several surgeons across many sites, given the relative infrequency of this type of surgery. A strength of this study is the inclusion of patients with risk factors for nonunion such as diabetes and neuropathy, and the inclusion of multiple surgeons and surgical sites, which suggests generalizability of the results.

In conclusion, rhPDGF-BB/β-TCP is a suitable graft material and viable alternative to autograft for revision rearfoot arthrodesis, even in higher-risk patients, without the pain and morbidity associated with harvesting of autograft.

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