The Open Orthopaedics Journal
DOI: 10.2174/0118743250283784231211111719, 2024, 18, e18743250283784

ISSN: 1874-3250
1

RESEARCH ARTICLE **OPEN ACCESS**

Ankle Fusion Rates using Composite Peptide-enriched Bone Graft

Luke S. McKinnon[1], Michael J. Symes[1], Andrew Wines[1] and Rajat Mittal[2,*]

[1]*Sydney Orthopaedic Foot and Ankle Research Institute (SOFARI), St Leonards, Australia*
[2]*Department of Orthopaedics and Trauma Surgery, Royal North Shore Hospital, St Leonards, NSW, Australia, Suite 10, Westmead Private Hospital, Cnr of Mons and Darcy Road, Westmead NSW 2145; Australia*

Abstract:

Introduction: Joint fusion is a widely accepted treatment option for debilitating arthritis and deformity in the foot and ankle. Autologous bone grafting has long been accepted as the gold standard form of bone grafting; however, it can still be associated with non-union. This study aims to investigate joint fusion rates using Composite Peptide Enhanced Bone Graft (CPEBG) as an adjunct during ankle fusion surgery.

Methods: Data was collected retrospectively for patients over the age of 18 years, undergoing ankle fusion between June 2016 and August 2020 with autologous bone graft and CPEBG. All patients had their primary or secondary procedure performed by a single surgeon with follow-up at 6 and 12 months post-operatively. Data included baseline demographic data and procedural characteristics. The primary endpoint was to assess joint union at 6 and 12 months, respectively. Secondary objectives included post-operative pain, mobility and the use of walking aids.

Results: Radiographic union rates for the primary group were 40/48 (83%) and 43/48 (90%) at 6 and 12 months and 2/3 (67%) and 3/3 (100%) at 6 and 12 months for the secondary group, respectively. The overall non-union rate for primary ankle fusions was 8%, while no non-unions were observed in the secondary group.

Conclusion: CPEBG in foot and ankle fusion procedures yields similar union rates compared to other graft options. Further well-designed randomised control trials are warranted to confirm these findings.

Keywords: Ankle fusion, Bone graft, Foot, Ankle joint, Pain, Walking aids.

*Address correspondence to this author at the Department of Orthopaedics and Trauma Surgery, Royal North Shore Hospital, St Leonards, NSW, Australia, Suite 10, Westmead Private Hospital, Cnr of Mons and Darcy Road, Westmead NSW 2145; Australia; E-mail: rajatmittal.research@gmail.com

Cite as: McKinnon L, Symes M, Wines A, Mittal R. Ankle Fusion Rates using Composite Peptide-enriched Bone Graft. Open Orthop J, 2024; 18: e18743250283784. http://dx.doi.org/10.2174/0118743250283784231211111719

Received: September 23, 2023
Revised: November 06, 2023
Accepted: November 14, 2023
Published: February 12, 2024

1. INTRODUCTION

Joint fusion is an appropriate surgical treatment option for end-stage arthritis of the ankle joint. The purpose of ankle fusion procedures is to achieve a bony union between the tibia and talus with appropriate alignment to alleviate debilitating pain and improve mobility [1]. To assist in achieving fusion of the tibiotalar joint, bone graft augment is commonly utilised to facilitate bony union. Despite the best treatment, incidences of non-union can occur, particularly in the presence of known risk factors, including avascular necrosis, prior infection, smoking, varus malalignment and uncontrolled diabetes mellitus [2, 3]. There are several sources of autologous bone grafts, including iliac crest, tibia or calcaneus; however, they can result in a physical and monetary cost to the health system and the patient [4]. They are also associated with morbidity, and complications can include infection, neurological injury, hematomas, along with ongoing pain [5-7]. A composite peptide-enhanced bone graft (CPEBG)

has been used successfully in spine surgery [8, 9]. There is potential for CPEBG to be used in foot and ankle surgery [10].

Recent studies have demonstrated similar union rates in ankle and hindfoot arthrodesis using rhPDGF/β-TCP (recombinant human platelet-derived growth factor with beta-tricalcium phosphate) compared to autologous bone graft [11]. To the best of our knowledge, there are no studies examining the union rates in ankle fusion procedures using CPEBG. We hypothesised that in patients undergoing both primary and secondary ankle fusion procedures with CPEBG bone augment, overall fusion rates would yield similar results to that described in the literature.

2. MATERIALS AND METHODS

This was a retrospective study of patients over the age of 18 who underwent ankle fusion procedures using CPEBG. The CPEBG used in this study was an i-FACTOR putty (Cerapedics Inc, Westminister, Colorado) CPEBG. This specifically engineered form of bone graft comprises of an anorganic bone mineral (ABM) derived from hydroxyapatite enriched with a P-15 peptide. The ABM component acts like a scaffold for bony ingrowth. P-15 is a 15 amino acid peptide that is found in type 1 human collagen. This peptide acts as an attachment factor for osteogenic precursor cells to promote osteogenesis [8]. All operations were performed by a fellowship-trained orthopaedic surgeon between June 2016 and August 2020.

Upon ethics approval, data collected included baseline patient demographic data (age, sex, co-morbidities), operative data (side operated, operation performed), follow-up data (subjective pain, post-operative limp and use of mobility aids), adverse events and radiographic data at 6 and 12 months.

2.1. Primary and Secondary Groups

All patients who underwent their index operation with the treating surgeon comprised of the primary surgical group. Patients undergoing revision ankle arthrodesis, where the index procedure was performed by another surgeon, comprised the secondary group. We analysed groups separately to determine overall rates of fusion at given time points.

Our primary endpoint was the confirmation of osseous union by radiographic or clinical criterion. Osseous union was defined by more than 50% bone bridging of the ankle joint on orthogonal plain radiographs. Radiographs were assessed independently by 2 fellowship-trained orthopaedic surgeons not involved in the surgery. All patients with 12-month radiographs had a 6-month radiograph. We used the last observation carried forward for the radiograph assessment for missing data. As per our routine practice, patients who achieved radiographic union and symptom-free at 6 months were not necessarily followed up at 12 months. Any discrepancies were resolved through discussion and with the involvement of a third fellowship-trained orthopaedic surgeon as required. Other imaging modalities, such as (computed tomography (CT) or magnetic resonance imaging (MRI) were not assessed.

Secondary objectives of this study included functional outcomes and complications from surgery. These outcomes were assessed at 6 and 12-month follow-up. Functional outcomes included patient-reported pain, the presence of a limp when mobilising, the use of mobility aids including crutches, walking frame and any post-operative complications (superficial/deep infection, deep vein thrombosis (DVT), pulmonary embolism (PE), need for repeat operation or hardware removal). We constitute a limp as being a deviation in an age-appropriate cyclical and symmetrical gait pattern whereby individuals displayed a shortened stance phase relative to the swing phase [12].

2.2. Surgical Approach

Procedures were performed in a standard fashion in compliance with hospital protocols. Patients received either a general or regional anaesthetic at the discretion of the anaesthetist, along with the administration of intravenous antibiotics. All procedures were performed with a standard open anterior approach to the ankle. The joint surfaces were prepared by denuding the cartilage. Bone graft was harvested from the ipsilateral calcaneus, mixed with CPEBG and inserted into the joint (50/50 ratio). Medial and lateral headless compression screws, along with an anterolateral ankle plate, were used to fix the joint. All patients were then placed in a short leg plaster of Paris back-slab and instructed not to weight bear for at least 6 weeks post operatively. The use of venous thromboembolism (VTE) prophylaxis was instructed for the duration of the non-weightbearing period.

3. RESULTS

A total of 48 patients were included in the primary group and 3 patients in the secondary group.

Patient demographics are presented in Table **1**. Within the primary group, 44% of patients had at least one co-morbidity, with hypertension most common at 31%. Other comorbidities prevalent within the primary group included inflammatory conditions (rheumatoid arthritis, Crohn's disease, ulcerative colitis, and systemic lupus erythema) and mental health conditions (*e.g*. depression, anxiety, bipolar disorder, and schizophrenia), which were present in 11% of patients respectively. Of the 3 patients in the secondary group, 1 patient had a prior DVT, and 1 patient had diabetes mellitus. There was 1 smoker in the primary group. No patients in the primary or secondary group had a diagnosis of Charcot neuroarthropathy.

Radiographic union rates for the primary group at at 6 & 12-month follow-up was 40/48 (90%) respectively. In our secondary group, 2/3 (67%) showed evidence of radiographic union at 6 months follow up. All secondary ankle fusion procedures united at 12 months follow up.

Complications for the primary and secondary groups are presented in Tables **2** and **3**, respectively. In particular, the overall non-union rate in our primary group

using clinical data was 8% after 12 months. The causes of repeat surgery included infections and non-union. In the primary group at 6 and 12 months, the pain was reported in 34/39 (87%) and 22/32 (69%), while 25/35 (71%) and 24/32 (75%) patients mobilised with a limp, respectively. The use of mobility aids decreased from 6/37 (16%) to 2/32 (6%).

Table 1. Patient demographics.

Demographics	Primary*	Secondary
Age, years (sd)	55 (15)	48 (16)
BMI (sd)	31 (4.5)	31 (-)
Side, n Right (%)	19/40 (48)	2/3 (67)
Smoking, n (%)	1/32 (3)	0/3 (0)
Comorbidity, n (%)	17/39 (44)	2/3 (67)
Hypertension, n (%)	12/39 (31)	0/3 (0)
Diabetes mellitus, n (%)	3/35 (9)	1/3 (33)
Prior DVT, n (%)	2/38 (5)	1/3 (33)
Inflammatory, n (%)	4/38 (11)	0/3 (0)
Mental health, n (%)	7/39 (18)	0/3 (0)

Note: * Demographic data not available for all patients.

Table 2. Results (primary group).

-	6 Months (%)	12 Months (%)
Pain, n (%)[a]	34/39 (87)	22/32 (69)
Limp, n (%)[b]	25/35 (71)	24/32 (75)
Mobility aid, n (%)[c]	6/37 (16)	2/32 (6)
Complications, n (%)	11/39 (28)	8/33 (24)
Superficial infection, n (%)	1/39 (3)	1/33 (3)
Deep infection, n (%)	2/39 (5)	1/33 (3)
DVT/PE, n (%)	0/39 (0)	0/33 (0)
Repeat Surgery, n (%)	11/39 (28)	7/33 (21)
Non Union, n (%)	3/39 (8)	2/33 (6)

Note: [a] none/mild pain symptoms.
[b] patients walking with a limp.
[c] patients using a walking stick/crutch/walker.

There were no non-unions noted in the secondary group. All 3 patients reported pain at 6 months (3/3, 100%), with 1 patient with ongoing pain at 12 months (1/3,33%). No patients presented with a limp at follow-up (0/2, 0% & 0/3, 0%), and 1 patient required the use of a mobility aid at 6 months only (1/3, 33% & 0/3, 0%). There was no correlation between complications and patient demographics in both groups.

4. DISCUSSION

The use of bone autologous bone graft (ABG) and bone graft substitutes have long been used to reduce the risk of non-union when performing arthrodesis in the foot and ankle joint. Our rates of radiographic ankle fusion were 83% and 90% at 6 & 12 months, respectively. Our overall clinical non-union rate was 8%.

This is comparable to non-union rates described by Haddad *et al*. [13]. They conducted a meta-analysis of 1262 ankle arthrodesis procedures (use of bone graft not specified) with an overall non-union rate of 10%.

DiGiovanni *et al*. conducted a study of 414 patients that examined the utility of recombinant human platelet-derived growth factor with beta-tricalcium phosphate matrix in ankle and hindfoot fusions with radiographic union rates of 61% and 67% and 6 and 12 months, respectively. This was compared to the use of ABG, which demonstrated similar rates of 66% and 65% at respective time periods [14]. To our knowledge, DiGiovanni's study is the largest multicentre randomised control trial to date examining rates of ankle and hindfoot fusion; however, the exact number of isolated ankle fusion procedures was not reported.

The utility of CPEBG is further substantiated by Arnold *et al*. noninferiority trial comparing the efficacy of i-FACTOR bone graft to autologous bone graft during anterior cervical discectomy and fusion procedures with both bone graft modalities showing similar rates of fusion at 12 and 24 months postoperatively [8]. The utility of a similar P-15 bone graft substitute has further been described for the management of long bone non-union by Gomar *et al*., with 90% (20 out of 22) patients demonstrating radiographic union [15].

Majority of patients had mild or minimal pain at both 6 and 12 months in both groups (as described in Tables **1**-**3** for the 6 and 12-month outcomes, respectively). These outcomes are similar to those described by Chou *et al*., assessing tibio-talo-calcaneal fusion. 84% of patients had mild/no pain after an average of 2 years follow. Chou *et al*. also noted that 64% of patients walked with a limp [16]. Davies et al. noted that 70% of patients had none or mild pain symptoms after a subtalar fusion [17]. Another study noted that the most patients were predominantly pain-free; however, this was after 5 years of follow-up following a triple arthrodesis [18].

Table 3. Results (secondary group).

-	6 Months (%)	12 Months (%)
Pain [a]	3/3 (100)	1/3 (33)
Limp [b]	0/2 (0)	0/3 (0)
Mobility aid [c]	1/3 (33)	0/3 (0)
Complications	0/3 (0)	0/3 (0)
Superficial infection	0/3 (0)	0/3 (0)
Deep infection	0/3 (0)	0/3 (0)
Repeat Surgery	0/3 (0)	0/3 (0)
Non Union	0/3 (0)	0/3 (0)

Note: [a] none/mild pain symptoms.
[b] patients walking with a limp.
[c] patients using a walking stick/crutch/walker.

There are various reasons for the increase in the number of patients presenting with a limp. These included patients undergoing repeat surgeries, delayed wound healing and delayed osseous union, and they were asked not to bear full weight. The reason for the increased percentage of patients limping at 12 months *vs* 6 months is the increased loss to follow-up at 12 months. We used the method of the last observation carried forward.

5. STRENGTHS AND LIMITATIONS

This is the first study to examine the efficacy of i-FACTOR CPEBG in ankle fusion procedures. To our knowledge, this is the largest single-centre retrospective analysis investigating isolated ankle fusion rates using CPEBG, demonstrating comparable results to traditional bone grafting options as described in the literature. The advantage of this study is that all procedures were performed by a single surgeon. All patients were followed up by a single surgeon post-operatively, allowing for consistency in reported patient clinical progress and operative outcomes.

This study experienced limitations with patient loss to follow-up and those associated with a retrospective study. Patients who were deemed radiographically united with minimal pain were not routinely followed up at 12 months. Of those patients that were followed up, 6- and 12-month radiographs were not always available. Due to the retrospective nature of this study, there is a lack of validated patient-reported outcomes, including overall satisfaction and functional outcomes. The inherent limitations with plain radiographs include operator-dependent views, beam obliquity, determining bony overlap and interruption of views with existing hardware. Previous studies have demonstrated poor correlation of CT scans and plain radiographs, with the latter imaging technique leading to an overestimation of the degree of bony union when compared to CT [19]. Our study did not conduct CT scans as routine practice, and thus, this was not included in the current study.

CONCLUSION

Our results show that using CPEBG as an adjunct in foot and ankle fusion procedures has similar union rates to other graft options. Further well-designed randomised control trials are warranted to confirm these findings.

LIST OF ABBREVIATIONS

CPEBG	=	Composite Peptide Enhanced Bone Graft
ABM	=	Anorganic Bone Mineral
MRI	=	Magnetic Resonance Imaging
DVT	=	Deep Vein Thrombosis
PE	=	Pulmonary Embolism
VTE	=	Venous Thromboembolism

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the St. Vincent's Hospital Human Research Ethics Committee (No. 2021/ETH00371).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Individual consent for this retrospective analysis was waived.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

This study was indirectly funded by Cerapedics.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Yasui Y, Hannon CP, Seow D, Kennedy JG. Ankle arthrodesis: A systematic approach and review of the literature. World J Orthop 2016; 7(11): 700-8. http://dx.doi.org/10.5312/wjo.v7.i11.700 PMID: 27900266

[2] Arner JW, Santrock RD. A historical review of common bone graft materials in foot and ankle surgery. Foot Ankle Spec 2014; 7(2): 143-51. http://dx.doi.org/10.1177/1938640013516358 PMID: 24425807

[3] Shibuya N, Humphers JM, Fluhman BL, Jupiter DC. Factors associated with nonunion, delayed union, and malunion in foot and ankle surgery in diabetic patients. J Foot Ankle Surg 2013; 52(2): 207-11. http://dx.doi.org/10.1053/j.jfas.2012.11.012 PMID: 23313498

[4] Fitzgibbons TC, Hawks MA, McMullen ST, Inda DJ. Bone grafting in surgery about the foot and ankle: indications and techniques. J Am Acad Orthop Surg 2011; 19(2): 112-20. http://dx.doi.org/10.5435/00124635-201102000-00006 PMID: 21292934

[5] St John TA, Vaccaro AR, Sah AP, *et al*. Physical and monetary costs associated with autogenous bone graft harvesting. Am J Orthop 2003; 32(1): 18-23. PMID: 12580346

[6] DeOrio JK, Farber DC. Morbidity associated with anterior iliac crest bone grafting in foot and ankle surgery. Foot Ankle Int 2005; 26(2): 147-51. http://dx.doi.org/10.1177/107110070502600206 PMID: 15737257

[7] Sen MK, Miclau T. Autologous iliac crest bone graft: Should it still be the gold standard for treating nonunions? Injury 2007; 38(1): S75-80. http://dx.doi.org/10.1016/j.injury.2007.02.012 PMID: 17383488

[8] Arnold PM, Sasso RC, Janssen ME, *et al*. i-Factor™ bone graft *vs* autograft in anterior cervical discectomy and fusion: 2-year follow-up of the randomized single-blinded food and drug administration investigational device exemption study. Neurosurgery 2018; 83(3): 377-84. http://dx.doi.org/10.1093/neuros/nyx432 PMID: 28945914

[9] Jacobsen MK, Andresen AK, Jespersen AB, *et al*. Randomized double blind clinical trial of ABM/P-15 *versus* allograft in noninstrumented lumbar fusion surgery. Spine J 2020; 20(5): 677-84. http://dx.doi.org/10.1016/j.spinee.2020.01.009 PMID: 32001384

[10] Lauweryns P, Raskin Y. Prospective analysis of a new bone graft in lumbar interbody fusion: Results of a 2- year prospective

clinical and radiological study. Int J Spine Surg 2015; 9: 2. http://dx.doi.org/10.14444/2002 PMID: 25709887

[11] Seow D, Yasui Y, Dankert JF, Miyamoto W, Calder JDF, Kennedy JG. Limited evidence for biological adjuvants in hindfoot arthrodesis. J Bone Joint Surg Am 2021; 103(18): 1734-43. http://dx.doi.org/10.2106/JBJS.20.01475 PMID: 34191761

[12] Auerbach N, Tadi P. Antalgic Gait in Adults. StatPearls. Treasure Island (FL): StatPearls Publishing 2022.

[13] Haddad SL, Coetzee JC, Estok R, Fahrbach K, Banel D, Nalysnyk L. Intermediate and long-term outcomes of total ankle arthroplasty and ankle arthrodesis. A systematic review of the literature. J Bone Joint Surg Am 2007; 89(9): 1899-905. http://dx.doi.org/10.2106/00004623-200709000-00002 PMID: 17768184

[14] DiGiovanni CW, Lin SS, Baumhauer JF, *et al*. Recombinant human platelet-derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/β-TCP): An alternative to autogenous bone graft. J Bone Joint Surg Am 2013; 95(13): 1184-92. http://dx.doi.org/10.2106/JBJS.K.01422 PMID: 23824386

[15] Gomar F, Orozco R, Villar JL, Arrizabalaga F. P-15 small peptide bone graft substitute in the treatment of non-unions and delayed union. A pilot clinical trial. Int Orthop 2007; 31(1): 93-9. http://dx.doi.org/10.1007/s00264-006-0087-x PMID: 16761146

[16] Chou LB, Mann RA, Yaszay B, *et al*. Tibiotalocalcaneal arthrodesis. Foot Ankle Int 2000; 21(10): 804-8. http://dx.doi.org/10.1177/107110070002101002 PMID: 11128009

[17] Davies MB, Rosenfeld PF, Stavrou P, Saxby TS. A comprehensive review of subtalar arthrodesis. Foot Ankle Int 2007; 28(3): 295-7. http://dx.doi.org/10.3113/FAI.2007.0295 PMID: 17371651

[18] Beischer AD, Brodsky JW, Polio FE, Peereboom J. Functional outcome and gait analysis after triple or double arthrodesis. Foot Ankle Int 1999; 20(9): 545-53. http://dx.doi.org/10.1177/107110079902000902 PMID: 10509680

[19] Coughlin MJ, Grimes JS, Traughber PD, Jones CP. Comparison of radiographs and CT scans in the prospective evaluation of the fusion of hindfoot arthrodesis. Foot Ankle Int 2006; 27(10): 780-7. http://dx.doi.org/10.1177/107110070602701004 PMID: 17054877