Orthobiologics in Foot and Ankle Arthrodesis Sites: A Systematic Review

February 2020

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

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Veterans Health Administration
Health Services Research & Development Service

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

Recommended citation: ***Example:*** Greer N, Yoon P, Majeski B, Wilt TJ. Orthobiologics in Foot and Ankle Arthrodesis Sites: A Systematic Review. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-009; 2020. Available at: https://www.hsrd.research.va.gov/publications/esp/reports.cfm.

This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the Minneapolis VA Medical Center, Minneapolis, MN, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Jeffrey Whitaker, DPM, for the purpose of determining the clinical and cost-effectiveness of orthobiologics for foot and ankle arthrodesis surgery compared to no orthobiologics. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

Jeffrey Whitaker, DPM
Chair, Podiatric Surgery Surgical Advisory Board
National Surgery Office

Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Samuel B. Adams, Jr, MD
Orthopedic Surgery
Duke University School of Medicine

Rodney Stuck, DPM
Section Chief, Podiatry – Surgical Service
Hines VA Medical Center

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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INTRODUCTION

Arthrodesis of the ankle, hindfoot, and midfoot joints is an operative treatment for patients with severe pain or disability caused by arthritis, degenerative joint disease, trauma, congenital deformity, Charcot neuropathy, and other conditions.[1,2] However, reported rates of nonunion following foot and ankle arthrodesis range from 0 to 36% with an average of 10 to 11%.[3-6] The observed variability is likely due, in part, to varying definitions of nonunion including how nonunion is evaluated (*ie*, radiographs, computed tomography (CT) scans, or clinically) and the degree of bone bridging required to classify an outcome as union versus nonunion.[3,4,6]

Nonunion following arthrodesis surgery is associated with poor function, disability, and the potential need for revision surgery.[4,7-9] A number of factors have been reported to be associated with nonunion including patient factors (*eg*, smoking, diabetes, alcohol consumption, low bone mineral density, age, obesity, rheumatoid arthritis, immunocompromised status, employment status, and certain medications), local factors (*eg*, infection, vascularity, bone defects or instability at the fusion site soft tissue injury, and revision arthrodesis procedure), and surgical factors (*eg*, use of sufficient graft material and high-volume vs low-volume surgeons).[4,7-10]

Orthobiologics are biologically derived materials that may be used, in the context of arthrodesis, to promote bone formation and union at the arthrodesis site.[6,11] Autograft, harvested from the iliac crest, tibia, calcaneus, or other sites, is considered the "gold standard" orthobiologic given that it possesses all 3 of the critical properties for bone healing: osteoconduction (providing a matrix or scaffold), osteoinduction (providing proteins and other factors to stimulate stem cells to differentiate into cells that can form bone), and osteogenesis (bone formation).[2,10,11] Successful osteoconduction, osteoinduction, and osteogenesis results in osteointegration – the incorporation of the bone graft with the existing bone.[12,13]

Autograft has the advantages of minimizing risk of an immunologic response or infection that might occur with a donor product and is available at no cost (other than costs associated with harvesting the graft). However, the quantity of graft material is limited and there are potential complications including the need for a separate incision site if a distant harvest site is chosen, longer operating time, nerve or vascular damage at the harvest site, and stress risers resulting in increased risk of bone fracture.[2,5,10,11] To date, there has not been a randomized trial comparing autograft to no graft.[2]

As a result of the potential complications associated with harvesting autograft, other orthobiologic products have been considered for use in arthrodesis. Of interest for this review are non-structural products including osteoinductive products (*eg,* platelet-derived growth factor [PDGF], demineralized bone matrix [DBM], bone morphogenetic proteins [BMP], platelet-rich plasma [PRP]) and osteogenic products (*eg,* bone marrow aspirate [BMA]).[5] Concerns with manufactured products include variability in manufacturing and differences across products in the same class due to proprietary preparation methods.[6,10]

Recombinant human PDGF (rhPDGF-BB), combined with beta-Tricalcium Phosphate (β-TCP) - an osteoconductive material, is a Food and Drug Administration (FDA) approved, bioengineered

product for hindfoot and ankle fusions in the US.[5,11,14] Although there are concerns about the increased risk of cancer based on studies of a topical form of rhPDGF-BB used for chronic wounds (becaplermin gel), recent studies comparing rhPDGF-BB/β-TCP to autograft for hindfoot or ankle arthrodesis found fewer or similar rates of serious treatment-emergent adverse events in the rhPDGF-BB/β-TCP group.[15,16]

DBM is an allograft product developed from bone harvested from cadavers. Through processing, some of the osteoinductive capacity of bone is lost.[5,6] DBM is used in filling bone defects, often in combination with another material.

BMPs are growth factors that influence the differentiation and proliferation of stem cells to bone-forming cells.[5,6,11,14] Recombinant human BMPs (rhBMP-2, rhBMP-7) are FDA-approved for use during spinal fusions, open tibial fractures, and long-bone nonunions and have been used off-label for arthrodesis. A major complication of BMP use is heterotopic bone formation, and use of BMPs is not recommended for the cervical spine.

PRP is derived from autologous blood. The end-product contains a highly concentrated volume of platelets that, when activated, release growth factors that promote healing and regeneration of soft tissues and bone.[5,14] There are many variables involved in the manufacturing process so it is difficult to make comparisons across studies.[6,14] PRP is not regulated by the FDA.

BMA or BMA concentrate (BMAC) contains stem cells and growth factors.[5,11,17] Harvesting of BMA is less invasive than graft harvesting. Typical harvest sites are the iliac crest, long bones, or calcaneus.[5] BMAC may be combined with an osteoconductive material.[11] The use of BMAC, to date, has largely been in fracture healing.[17]

The purpose of our review was to examine the evidence from studies comparing use of an orthbiologic to no orthobiologic in primary foot (forefoot and proximally) and ankle arthrodesis procedures. Our focus was on non-structural autogenous orthobiologics.

We addressed the following key questions:

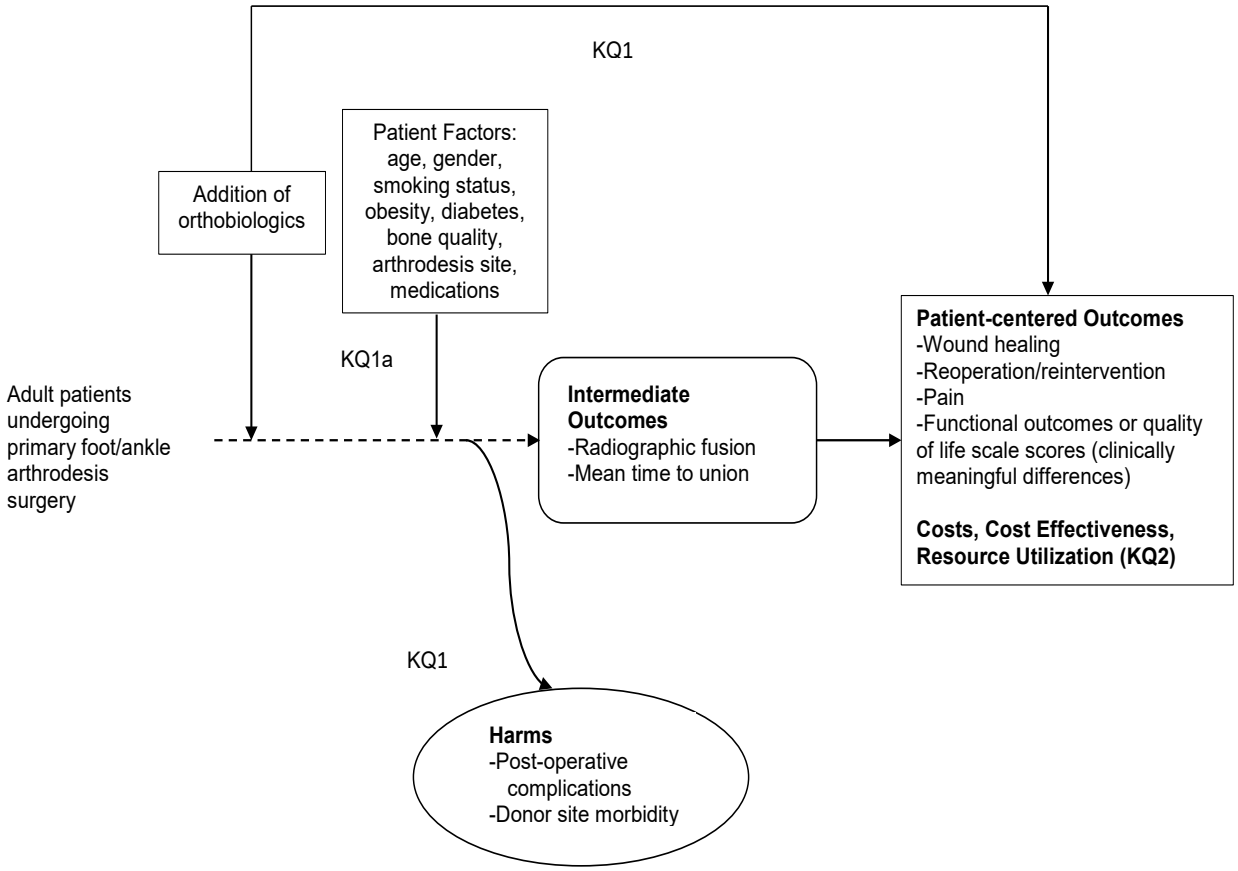
1) What are the effectiveness and harms of adding orthobiologics compared to no orthobiologics when performing primary foot/ankle arthrodesis surgery?

1a) Do effectiveness and harms vary by patient age, gender, smoking status, obesity, diabetes, bone quality, arthrodesis site, or use of medications that may impede healing (*eg,* immunosuppressives)?

2) What is the cost and/or cost-effectiveness (as reported in the literature) of adding orthobiologics compared to no orthobiologics when performing primary foot/ankle arthrodesis surgery?

The analytic framework (Figure 1) depicts the population, intervention, and outcomes of interest.

Figure 1. Analytic Framework



METHODS

TOPIC DEVELOPMENT

This topic was nominated by Jeffrey Whitaker, DPM, Chair of the Podiatric Surgery Surgical Advisory Board. The intended usage of the report was to inform best-practice guidelines for podiatric surgery in VHA. With input from Dr. Whitaker and Technical Expert Panel (TEP) members, we developed the key questions and scope for the review.

SEARCH STRATEGY

We searched Ovid MEDLINE, Embase, and the Cochrane Library from 1995 to July 2019. The MEDLINE search strategy (Appendix A) included Medical Subject Headings (MeSH) and title/abstract words for orthobiologics (*eg,* autografts, bone substitutes, platelet-derived growth factor, platelet-rich plasma), foot and ankle site (*eg,* foot joints, ankle joint) and arthrodesis. Searches of Embase and the Cochrane Library were conducted using similar search strategies. We also searched clinicaltrials.gov for recently completed or ongoing studies and reference lists of relevant systematic and narrative reviews and included studies for articles missed by our literature search.

STUDY SELECTION

Citations were entered into Distiller SR (Evidence Partners). Titles and abstracts were reviewed independently by 2 reviewers with a citation moving to full-text review if either reviewer considered the citation eligible. At full-text review, agreement of 2 reviewers was needed for study inclusion or exclusion. Disputes were resolved by discussion with input from a third reviewer, if needed.

We included randomized or controlled clinical trials, case series with concurrent controls, or pre- to post-intervention studies (*eg*. interrupted time series) that provided a comparison of the use of an orthobiologic of interest (see below) to no orthobiologic.

Population

Adults undergoing primary foot/ankle arthrodesis surgery (forefoot to ankle).

Intervention

Non-structural autogenous orthobiologics (autogenous bone graft, bone marrow aspirate, plasma products); synthetic products.

Comparator

No orthobiologic. Although we label this as a comparator, the studies included in our review were not designed as comparative studies. Most were retrospective reviews of medical records and study groups consisted of those who received an orthobiologic and those who did not, most often at the surgeon's discretion.

Outcomes

Patient-centered Outcomes: Wound healing, need for reoperation/reintervention, pain, clinically meaningful differences in functional outcome or quality of life scale scores (*eg*, American Orthopedic Foot and Ankle Society [AOFAS], Mazur).

Intermediate Outcomes: Radiographic fusion, mean time to union.

Costs, Cost Effectiveness, Resource Utilization: Patient costs, facility costs.

Harms: Post-operative complications (*eg*, scar pain, wound dehiscence, wound complications, neuritis, infection, amputation, malalignment, lateral impingement, mortality, venous thromboembolism); donor site morbidity (*eg*, hematoma formation, infection, chronic pain, neurological deficits, iatrogenic fractures).

We excluded studies not enrolling a population of interest (*eg*, Charcot foot, children); not evaluating an orthobiologic of interest; not involving a surgery of interest (*eg*, revision arthrodesis); involving a comparator other than no orthobiologic; using historical controls; or not reporting outcomes of interest. We also excluded case reports, animal or laboratory studies, papers describing a surgical approach but not reporting outcomes, and non-English publications.

DATA ABSTRACTION

We abstracted study characteristics (inclusion/exclusion criteria, orthobiologic used, patient demographics), patient-centered outcomes, intermediate outcomes, costs, and harms (see above). Studies were organized by orthobiologic used.

QUALITY ASSESSMENT

We used elements from the Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies[18] and Critical Appraisal Checklist for Case Series[19] to assess the quality of the studies (Appendix B). We describe the quality characteristics of the included studies.

DATA SYNTHESIS

Due to differences in orthobiologics used, methods of outcome assessment, and heterogeneity of the included populations (*eg,* reasons for arthrodesis, arthrodesis site, rationale for receiving or not receiving an orthobiologic), we narratively summarized the findings.

RATING THE BODY OF EVIDENCE

We did not formally rate the overall body of evidence. We describe limitations of the available evidence.

PEER REVIEW

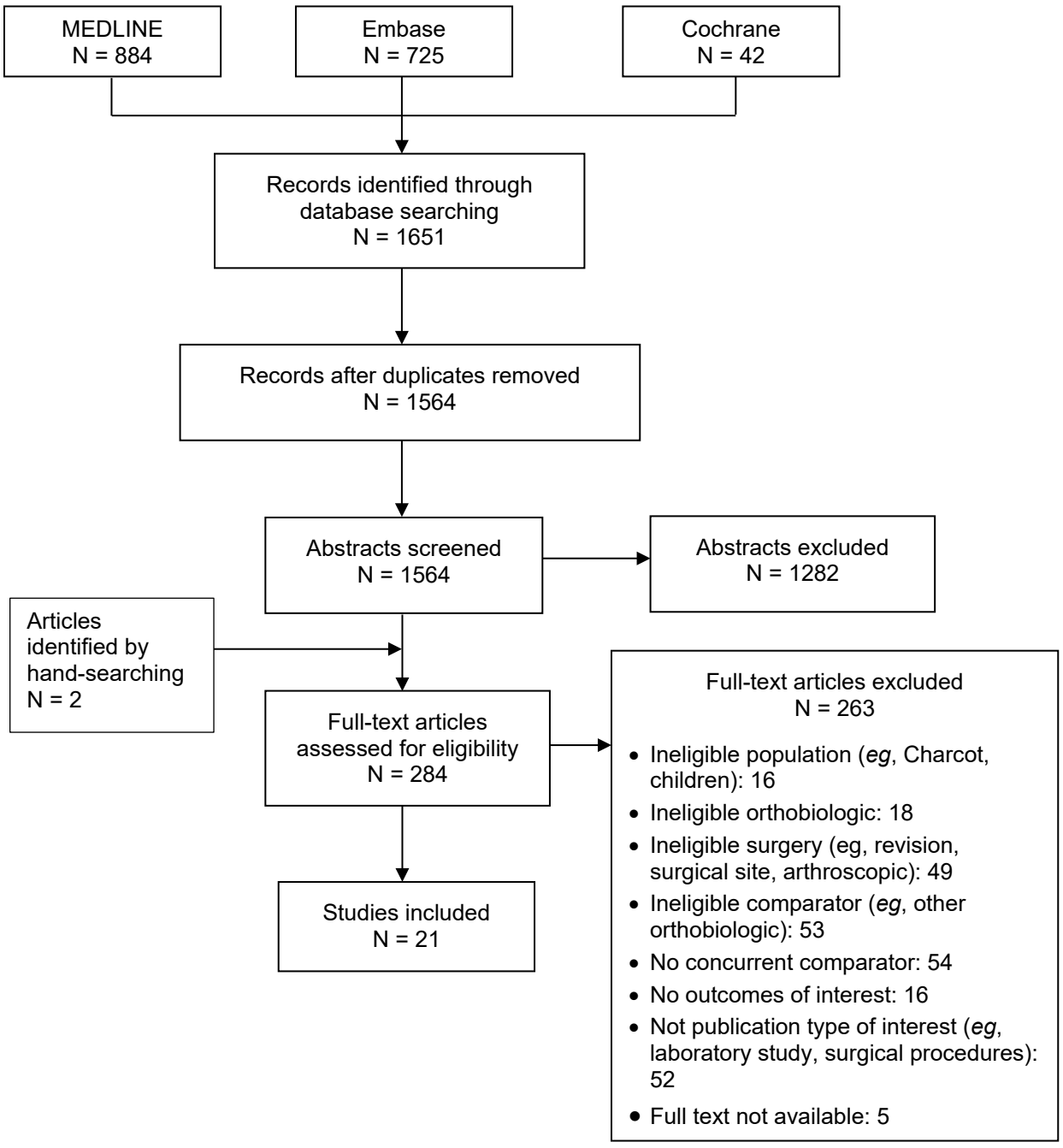
A draft version of this report was reviewed by content experts as well as clinical leadership. Reviewer comments and our responses are presented in Appendix C and the report was modified as needed.

RESULTS

LITERATURE FLOW

Figure 2 depicts the results of our abstract and full-text article review process. Our search of multiple databases yielded 1,651 citations. Removing duplicates resulted in 1,564 abstracts for review. Of those, 282 were identified for full-text review along with 2 articles identified from hand-searching. We excluded 263 articles, many of which involved a surgical procedure that was not of interest for our review or that did not have a no-graft comparator group, and included 21.

Figure 2: Literature Flow Chart



KEY QUESTION 1: What are the effectiveness and harms of adding orthobiologics compared to no orthobiologics when performing primary foot/ankle arthrodesis surgery?

KEY QUESTION 1A: Do effectiveness and harms vary by patient age, gender, smoking status, obesity, diabetes, bone quality, arthrodesis site, or use of medications that may impede healing (*eg*, immunosuppressives)?

Summary of Findings

Accurately assessing the effectiveness of orthobiologics is not possible due to poor methodological quality of studies. Most reports were small retrospective chart review studies with little controlling for patient factors (*eg,* health status, medications, severity of presentation) likely to affect intervention indication or effectiveness. No studies were designed specifically to assess the effect of orthobiologics versus no orthobiologics on outcomes following foot and ankle arthrodesis. Orthobiologics were typically used at a surgeon's discretion for patients judged to be at higher risk for non-union (*eg*, large bone defects, malalignment, or patient health-related factors). Few studies reported significant differences in outcomes between patients receiving orthobiologics and those not receiving orthobiologics, though most studies were small and statistically significant results could not be ruled out. Evidence was insufficient to assess whether effectiveness of orthobiologics varied by patient age, gender, smoking status, obesity, diabetes, bone quality, arthrodesis site, or use of medications that may impede healing due to limited reporting.

Overview of Studies

We identified 21 studies that reported a comparison of an orthobiologic to no orthobiologic in foot and ankle arthrodesis.[20,21,22-26,27,28,29,30,31,32-36,37,38,39,40] Orthobiologics included autologous bone graft or slurry and recombinant human bone morphogenetic protein (rhBMP-2), demineralized bone matrix (DBM), or platelet products alone or in combination with autologous graft (Table 1). The number of subjects ranged from 9 to 133, mean age was 50 years (range 28-62 years), 55% were male (range 13-80%), and follow-up periods ranged from 3 to 78 months (mean 32 months). Three studies reported that patients were followed until union.[21,22,34] There were 11 studies from the US, 5 from Asia, 3 from Europe, and 1 from Canada. One study did not report where the procedures were performed.[20] Additional study information including inclusion/exclusion criteria, description of the orthobiologics, and patient demographics is presented in Appendix D, Table 1.

Included studies were predominantly retrospective chart reviews; 4 provided a retrospective analysis of prospectively enrolled cases.[20,31,33,36] Seven studies, 5 using autologous bone graft or slurry,[21,25,27,38,40] 1 using rhBMP-2,[28] and 1 using DBM,[23] reported that an objective of the study was to evaluate the use of an orthobiologic.

Table 1. Orthobiologics and Number of Studies

Orthobiologic	Number of Studies	Sample Size Total (range)	Age (mean)	% Male (mean)
Autologous bone graft vs no graft	10	469 (9-133)	48	53
Remote autologous graft vs local graft	2	32 (15-17)	53	56
Local bone slurry vs no slurry	1	54	52	65
rhBMP-2 + graft vs rhBMP-2 only	2	117 (48-69)	52	56
DBM + graft vs no graft	1	88	57	20
Platelet products + femoral head allograft vs femoral head allograft	1	14	43	71
rhBMP-2 vs no orthobiologic	1	82	57	NR
DBM, Platelets, or BMP alone or in combination (some with bone graft) vs no orthobiologic	3	113 (16-57)	51	68 (2 studies reporting)

BMP=bone morphogenetic protein; DBM=demineralized bone matrix; NR=not reported

Table 2 provides an overview of the outcomes reported. All studies reported either fusion or time to fusion. Although we identified fusion as an intermediate outcome that would likely affect patient-centered outcomes such as pain, function, quality of life, and need for reoperation, there is consensus that fusion is an appropriate indicator of intervention effectiveness. A measure of functional ability or quality of life was reported in 10 of the 21 studies. Other outcomes of interest were rarely reported including need for reoperation (or amputation), wound complications or infections, and donor site morbidity.

Outcomes reported for each study are presented in Table 3. The studies are grouped by the orthobiologic/non-orthobiologic used. A check mark indicates that the outcome was reported by that study. An arrow indicates the direction of the effect with a neutral arrow (↔) signifying no difference between the orthobiologic and non-orthobiologic groups. Outcomes data for each study are reported in Appendix D, Tables 3-7.

Table 2. Orthobiologics and Outcomes Reported

Orthobiologic (Number of Studies)	Wound Healing	Need for Reoperation	Pain	Function or QoL	Fusion	Time to Fusion	Costs (patient or facility)	Wound Complications/ Infection	Donor Site Morbidity
Bone Graft vs no Graft (10)	1	2	2	8	9	5		2	1
Remote Graft vs Local (2)	1		1	1	2	1	1		
Bone Slurry vs No Slurry (1)		1			1				
rhBMP-2 + Graft vs rhBMP-2 (2)					1	2			
DBM + Graft vs No Graft (1)					1				
PRP vs No PRP (1)					1				
rhBMP-2 (1)					1			1	
Mixed Products (3)	1		2	1	3	3	1	1	
TOTALS	**3**	**3**	**5**	**10**	**19**	**11**	**2**	**4**	**1**

Other outcomes extracted: Mortality (no studies reporting), Amputation (2 studies reporting); Minimal Clinically Important Differences for Function or Quality of Life (no studies reporting)

BMP=bone morphogenetic protein; DBM=demineralized bone matrix; PRP=platelet-rich plasma; QoL=quality of life

Fusion/Time to Fusion

Fifteen of 19 studies reporting rate of fusion found no difference in fusion rates between the orthobiologic and non-orthobiologic groups. Studies used different methods of assessing fusion (*eg,* x-ray, CT, clinical) and had different criteria for defining fusion (Appendix D, Table 5). Three studies reported higher fusion in the orthobiologic group, including 1 that compared autologous bone graft with or without DBM to no graft (93% vs 72%),[23] and 1 that compared rhBMP-2 to no rhBMP-2 (92% vs 82%).[28] The third study reported a higher percentage of bridging with local bone slurry vs no slurry (94% vs 76%).[38] One study reported significantly fewer fusions (*ie*, more nonunion) in a group treated with rhBMP-2 plus autograft compared to rhBMP-2 only (79% vs 100%).[34]

Table 3. Orthobiologics – Summary of Outcomes

Author, Year, Study Design, Sample Size	Site(s)	Orthobiologic(s) Non-Orthobiologic	Wound Healing	Need for Reoperation/ Reintervention	Pain	Function/QoL (MCID)	Function/QoL Scale Scores	Radiographic Fusion	Time to Fusion	Costs (Patient/ Facility)	Wound Complications/ Infection	Mortality	Amputation	Donor Site Morbidity
Bone Graft vs No Graft (k=10)														
Abd-Ella, 2017[20] Prospective Case Series N=12	Ankle/ subtalar	Autogenous bone graft (n=9) No graft (n=3)	✓ ↔	✓[a]			✓ ↔	✓[a]						✓ ↔
Anderson, 2013[21] Retrospective Chart Review N=114	First metatarso-phalangeal joint	Autograft (local; reduced to cancellous bone chips) (n=62) End-to-end arthrodesis (n=52)					✓ ↔	✓ ↔	✓ ↔					
Cao, 2017[24] Retrospective Chart Review N=30	Talon-avicular	Autoallergic iliac bone graft (n=5) No bone graft (n=11)					✓ ↔	✓ ↔						
Chahal, 2006[25] Retrospective Chart Review N=88	Isolated subtalar	Local or iliac crest bone graft (n=46) No graft (n=20)						✓ ↔						
Chen, 1996[26] Retrospective Chart Review N=38 (40 ankles)	Tibiotalar	Tibial condyle graft (n=8 ankles) or sliding graft (n=7 ankles) No graft (n=25)					✓ ↔	✓ ↔			✓ ↔		✓ ↔	
Easley, 2000[27] Retrospective Chart Review N=174 (184 feet)	Isolated subtalar	Cancellous autograft (n=94 feet) No graft (n=39 feet)					✓ ↔	✓ ↔	✓ ↔					

Author, Year, Study Design, Sample Size	Site(s)	Orthobiologic(s) Non-Orthobiologic	Wound Healing	Need for Reoperation/ Reintervention	Pain	Function/QoL (MCID)	Function/QoL Scale Scores	Radiographic Fusion	Time to Fusion	Costs (Patient/ Facility)	Wound Complications/ Infection	Mortality	Amputation	Donor Site Morbidity
Holm, 2015[30] Retrospective Chart Review N=17	Subtalar	Autogenous bone (n=3) No orthobiologic (n=6)		✓ ↔	✓ ↔		✓ ↔	✓ ↔						
Lechler, 2012[31] Prospective Case Series N=30	Talon-avicular	Autologous spongious bone graft from iliac crest (n=6) No orthobiologic (n=24)			✓ ↔		✓ ↔		✓ ↔					
Yavuz, 2014[39] Retrospective Chart Review N=20 (21 feet) total	Subtalar	Cancellous autograft (iliac crest) (n=8) No graft (n=9)						✓ ↔	✓ ↔		✓ ↔			
Yildirim, 2015[40] Retrospective Chart Review N=31 (33 feet) total	Subtalar	Autograft (iliac crest) (n=16 feet) No graft (n=14 feet)					✓ ↔	✓ ↔	✓[b] ↓					
Remote Graft vs Local Graft (k=2)														
Patil, 2011[32] Retrospective Chart Review N=26	Subtalar	Autologous iliac crest bone graft (n=4) Local bone graft (n=13)			✓ ↔			✓ ↔						
Sun, 2019[36] Prospective Case Series N=15	Subtalar	Bone graft from iliac crest to supplement local graft (n=4) Local bone (n=11)	✓ ↔				✓ ↔	✓ ↔	✓ ↔	✓[c] ↑				

Author, Year, Study Design, Sample Size	Site(s)	Orthobiologic(s) Non-Orthobiologic	Wound Healing	Need for Reoperation/ Reintervention	Pain	Function/QoL (MCID)	Function/QoL Scale Scores	Radiographic Fusion	Time to Fusion	Costs (Patient/ Facility)	Wound Complications/ Infection	Mortality	Amputation	Donor Site Morbidity
Local Slurry vs No Slurry (k=1)														
Wheeler, 2009[38] Retrospective Chart Review N=54	CPT code 27870 (Arthrodesis Procedures on Leg & Ankle Joint)	Local bone slurry (n=32) No slurry (n=22)		✓ ↔				✓[d] ↑						
rhBMP-2 + Graft vs rhBMP-2 only (k=2)														
Bibbo, 2009[22] Retrospective Chart Review N=69 (112 fusion sites)	Ankle and hindfoot	rhBMP-2 (INFUSE®) and autogenous iliac crest bone graft (n=17 fusions) rhBMP-2 only (n=85 fusions)							✓ ↔					
Rearick, 2014[34] Retrospective Chart Review N=48 (51 cases, 83 sites) total	Foot or ankle	rhBMP-2 + autograft (14 sites) (local=11, iliac crest=2, calcaneus=1) rhBMP-2 only (60 sites)						✓[e] ↓	✓ ↔					
DBM + Graft vs No Graft (k=1)														
Buda, 2018[23] Retrospective Chart Review N=88 (189 joints)	Tarso-metatarsal	Autologous bone graft (n=37) Autologous bone graft + DBM (n=33) No graft (n=18)						✓[d] ↑						

Author, Year, Study Design, Sample Size	Site(s)	Orthobiologic(s) Non-Orthobiologic	Wound Healing	Need for Reoperation/ Reintervention	Pain	Function/QoL (MCID)	Function/QoL Scale Scores	Radiographic Fusion	Time to Fusion	Costs (Patient/ Facility)	Wound Complications/ Infection	Mortality	Amputation	Donor Site Morbidity
Platelet Products (k=1)														
Grunander, 2012[29] Retrospective Chart Review N=14 (16 feet)	Calcaneo-cuboid	Femoral head allograft and PRP (n=7 feet) Femoral head allograft alone (n=9 feet)						✓ ↔						
rhBMP-2 (k=1)														
Fourman, 2014[28] Retrospective cohort N=82	Ankle	rhBMP-2 (n=42) No rhBMP-2 (n=40)						✓[d] ↑			✓ ↔		✓ ↔	
Other/Mixed Products (k=3)														
Plaass, 2009[33] Prospective Case Series N=29	Tibiotalar	DBM (n=8) Platelet concentrate (n=1) Both (n=2) No orthobiologic (n=5)	✓[a]		✓[a]		✓[a]	✓ ↔	✓ ↔					
Rungprai, 2016[35] Retrospective Chart Review N=57 (60 feet)	Subtalar	Cancellous autograft (n=12) DBM + allograft (n=12) BMP + allograft (n=12) Platelet concentrator + allograft (n=7) No orthobiologic (n=6)						✓ ↔	✓ ↔					

Author, Year, Study Design, Sample Size	Site(s)	Orthobiologic(s) Non-Orthobiologic	Wound Healing	Need for Reoperation/ Reintervention	Pain	Function/QoL (MCID)	Function/QoL Scale Scores	Radiographic Fusion	Time to Fusion	Costs (Patient/ Facility)	Wound Complications/ Infection	Mortality	Amputation	Donor Site Morbidity
Weinraub, 2010[37] Retrospective Chart Review N=45	Combined subtalar and talonavicular	PRP (n=7) PRP/DBM (n=6) DBM (n=5) BMP (n=1) DBM/SC (n=1) PGC (n=1) PRP/SC (n=1) No orthobiologic (n=18)			✓[a]			✓ ↔	✓ ↔	✓[f] ↔	✓ ↔			

BMP=bone morphogenetic protein; DBM=demineralized bone matrix; MSC=mesenchymal stem cells; PGC=platelet gel concentrate; PRP=platelet-rich plasma, rhBMP-2=recombinant human bone morphogenetic protein-2; SC=stem cell

[a] Small n or few events – not able to interpret findings

[b] Significantly shorter time to fusion with orthobiologic

[c] Significantly longer operating time for iliac crest graft group

[d] Significantly greater fusion rate with orthobiologic

[e] Significantly more nonunions in rhBMP-2 + autograft group; all had history of nonunion

[f] No difference in surgery duration; no graft harvesting procedures

Including data from all orthobiologic products and arthrodesis sites, fusion rates ranged from 71% to 100% in the orthobiologic group (mean 93%) and from 0% to 100% (mean 85%) in the no-orthobiologic group. Removing one study with a 0% fusion rate in the no-orthobiologic group of 3 individuals,[20] the range was 44% to 100% (mean 90%) in the no-orthobiologic group.

All but 2 of the 15 studies reporting no difference between study groups reported fusion rates of 85% or higher for both groups. One exception was 1 study of iliac crest or local bone graft versus no graft for 66 isolated subtalar fusions related to primary or secondary osteoarthritis.[25] Smoking status was not reported for the orthbiologic/non-orthobiologic groups, but overall 43% had smoked at least 1 week before and after surgery. Diabetes was reported in 10% of the population. Fusion rates were 84% in the orthobiologic group and 65% in the non-orthobiologic group. The other exception was a study of PRP with femoral head allograft versus femoral head allograft alone for 14 patients undergoing calcaneocuboid distraction arthrodesis.[29] Fusion rates were 71% in the PRP group and 44% in the allograft group.

Time to fusion was reported in 11 studies. Three reported that time to fusion did not differ between the orthobiologic and non-orthobiologic groups but did not report actual times.[31,36,39] For the 8 studies reporting time to fusion, the mean was 12.2 weeks in both the orthobiologic and non-orthobiologic groups.[21,22,27,33-35,37,40] Only 1 study reported a significant difference in mean time to fusion – 14.4 weeks for 19 patients receiving iliac crest autograft versus 17.5 weeks for 14 patients receiving no graft for subtalar arthrodesis.[40]

Patient-centered Outcomes

The most frequently reported patient-centered outcome was a measure of functional status or quality of life (Appendix D, Table 4). None of the 10 studies reporting this outcome found a difference between the orthobiologic and non-orthobiologic groups.[20,21,24,26,27,30,31,33,36,40] Seven studies reported American Orthopedic Foot and Ankle Society (AOFAS) scores, a measure of function, pain, and alignment.[24,27,30,31,33,36,40] Three studies assessed patient satisfaction,[20,21,24] willingness to have the procedure again,[21] and ability to walk a long distance 6 months post-surgery.[24] One study used a clinical outcomes rating system.[26]

Other patient-centered outcomes of interest including wound healing, need for reoperation or reintervention, and pain were infrequently reported. Where reported, no differences were observed between the orthobiologic and non-orthobiologic groups (Appendix D, Tables 3 and 4)

Harms

Few studies reported harms. Only one study reported donor site morbidity, finding no instances among 12 patients undergoing ankle or subtalar arthrodesis with and without autograft.[20] Two studies reported amputation with each identifying 1 case in the non-orthobiologic group and no cases in the orthobiologic group, either autograft[26] or rhBMP-2.[28] Three studies reported infection with few cases and no significant differences between orthobiologic and non-orthobiologic groups.[26,28,39]

Quality of Evidence for Key Question 1

We did not formally rate risk of bias or quality of evidence. We evaluated each included study based on critical appraisal criteria for quasi-experimental studies and case series (Appendix B,

Appendix D, Table 2). Several characteristics of the studies suggest likely selection and detection bias.

Criteria for inclusion in the study were clearly defined in 16 of 21 studies (76%); however, only 48% (10 studies) reported complete inclusion (*ie,* including consecutive cases or all cases within a specified time period). Although 7 studies reported that a primary objective of the study was to evaluate the use of an orthobiologic, in 16 studies (76%), patients were treated with an orthobiologic at the surgeon's discretion – most often due to large bone defects, poor bone alignment, or patient risk factors for nonunion – and the evaluation of orthobiologic use was a retrospective analysis based on whether the product was used during the surgery. The remaining 5 studies did not report a reason why some patients received an orthobiologic and others did not. Only 4 studies (19%) reported that radiographs were reviewed by individuals unaware of whether or not patients received an orthobiologic. Five studies (24%) stated that reviews were not blinded while reporting of blinding/no blinding was unclear in 12 studies (57%). Five studies (24%) used CT scans to confirm fusion observed on radiographs.

KEY QUESTION 2: What is the cost and/or cost-effectiveness (as reported in the literature) of adding orthobiologics compared to no orthobiologics when performing primary foot/ankle arthrodesis surgery?

Summary of Findings

We found insufficient evidence to assess costs or cost-effectiveness of orthobiologics. Two studies reported operation time, finding longer times for procedures involving graft harvest but no difference in operation time when non-graft orthobiologic products were used.

Operation Time

Only 2 of our included studies reported a cost-related outcome.

One study, conducted in the US, included 40 patients who underwent combined subtalar joint and talonavicular joint arthrodesis.[37] The group treated with orthobiologics received non-graft products including platelet-rich plasma, demineralized bone matrix, stem cells, and bone morphogenetic protein alone or in combination. The mean duration of surgery ranged from 82 to 98 minutes for surgeries involving an orthobiologic product compared to 83 minutes for surgeries with no orthobiologic product.

A study from China of 15 minimally invasive subtalar arthrodesis procedures performed with local graft or local graft supplemented by graft harvested from the iliac crest reported mean operation times.[36] The mean operation time for procedures involving iliac crest harvest was longer than the operation time for procedures using only local graft (83.8 minutes vs 50.9 minutes, P<.01).

SUMMARY AND DISCUSSION

KEY FINDINGS

Accurately assessing effectiveness of orthobiologics is not possible due to poor methodological quality of studies. Most reports were small retrospective chart review studies with little controlling for patient factors (*eg,* health status, medications, severity of presentation) likely to affect intervention indication or effectiveness.

1. No studies were designed specifically to assess the effect of orthobiologics versus no orthobiologics on outcomes following foot and ankle arthrodesis. All studies evaluating orthobiologic effectiveness as a primary study objective were retrospective.

2. Orthobiologics were typically used at a surgeon's discretion for patients judged to be at higher risk for non-union (*eg*, large bone defects, malalignment, or patient health-related factors).

3. The greatest amount of information is on bone grafts. There is extremely limited information on other orthobiologics for foot and ankle arthrodesis.

4. All studies reported either radiographic or CT fusion, or time to fusion, and nearly half reported a measure of function or quality of life. Other outcomes of interest were infrequently reported, including donor site morbidity.

5. Few studies reported significant differences in outcomes between patients receiving orthobiologics and those not receiving orthobiologics, though most studies were small and statistically significant results could not be ruled out.

6. Evidence was insufficient to assess whether effectiveness of orthobiologics varied by patient age, gender, smoking status, obesity, diabetes, bone quality, arthrodesis site, or use of medications that may impede healing due to limited reporting. Several studies addressed risk factors for healing but did not report results for orthobiologic and no orthobiologic subgroups.

7. Evidence was insufficient to assess costs or cost-effectiveness of orthobiologics. Two studies reported operation time, finding longer times for procedures involving graft harvest but no difference in operation time when non-graft orthobiologic products were used.

8. Although randomized trials are the gold standard for effectiveness research, a randomized trial would be difficult due to variability in patient health and bone structure factors.

9. Data registries, including VA-NSQIP in combination with other VA databases, might provide useful information by evaluating outcomes after carefully controlling for patient factors likely to influence intervention indication and outcomes. It may be possible to also merge this information with VA cost data to more accurately assess the cost, cost-effectiveness, and budget impact of orthobiologics.

10. Some orthobiologics may be effective in, and are FDA-approved for, spinal fusions or open tibial fractures. It is not known if these findings are applicable to foot and ankle arthrodesis.

11. Given the current evidence, we suggest consideration of utilization review and approval prior to use. This would focus orthobiologic use and a potential second surgical procedure on patients and/or arthrodesis sites of greatest risk of nonunion. Providers and policymakers should be aware of the cost and possible morbidity associated with widespread use of orthobiologics given the insufficient to low-strength evidence of benefit – in particular, mostly radiographic rather than clinical outcomes.

DISCUSSION

No orthobiologic can replace good surgical technique and good academic decision-making.[10] Surgeons can optimize success by taking into consideration the risk factors for nonunion when selecting patients for orthobiologics, emphasizing the importance of compliance with post-surgery protocols, and using sound surgical principles such as careful preparation of opposing bone surfaces, compression across the arthrodesis site, and external fixation where needed.[6,13]

As new orthobiologics are introduced (likely at higher costs), surgeons need to critically analyze any product information and research results including risks, benefits, cost, surgical complexity (including the possibility of an additional surgical procedure for bone graft harvesting that may involve donor site morbidity), and volume of material available.[6,11,13] There is a need for more rigorous outcome data to compare fusion rates of each product as well as one product versus another and different products within the same class (different due to proprietary manufacturing processes).[6]

A survey of North American and Canadian orthopedic foot and ankle surgeons was designed to determine clinical and radiographic factors associated with the decision to use supplemental bone graft.[1] The survey was completed by 48 of 66 (73% response rate) surgeons (representing academic and private practice) who received the survey. It is important to note that the surgeons were all involved in a large clinical trial of an autograft substitute. The most frequently reported clinical factors were nonunion (*ie,* regarding use of graft in a revision surgery), nonunion of an adjacent joint, smoking history, use of medications known to interfere with bone healing, and vitamin D deficiency. Frequently reported radiologic factors included nonunion, avascular necrosis, evidence of potential incongruous apposition, radiographic evidence of bone loss, osteoporosis, or post-trauma with subchondral collapse. There was variation in the sample with regard to the weighting of the clinical and radiographic factors when deciding whether to use bone graft although all surgeons reported that they considered both types of information to some degree.

Two recent systematic reviews noted that few studies reported on use of autograft versus no autograft.[2,41] Müller et al included studies comparing cortical or cancellous autologous bone grafts with any structural or non-structural substitute.[41] Both prospective and retrospective controlled trials were included provided a minimum of 20 patients were enrolled. The review included 10 studies; quality was low. The authors concluded that “structural allografts appear to be at least non-inferior to autologous grafts” for union in hindfoot arthrodesis but called for RCTs with larger sample sizes. Only one of the studies from the Müller et al review, a study that also included a non-graft group,[27] was included in our review.

Lareau et al included 159 papers reporting union and nonunion rates associated with the use of autograft, allograft, or no bone graft in arthrodesis, osteotomies, and treatment of nonunions.

They excluded studies that supplemented bone graft insertion with a bone graft substitute or other orthobiologic, studies in children younger than 10 years of age, non-English language articles, case reports with fewer than 4 patients, and use of xenograft or any vascularized bone graft.[2] Of relevance to our review, the authors presented data from 2213 patients in 70 studies who received cancellous autograft and from 1208 patients in 50 studies who did not receive a bone graft. Relative to no graft, the odds ratio for union with cancellous autograft was 1.39 (95%CI 0.92, 2.1; P=.11). The probability of union was 93.7% with cancellous autograft and 91.4% for no graft. When the analysis was limited to studies with both cancellous autograft and no graft groups, the union rates were 95.1% and 91.9% for cancellous autograft and no graft, respectively. The odds ratio was 1.79 (95%CI 0.91, 3.3; P=.09). The authors did not provide results by type of surgical procedure. They also attempted to evaluate the potential impact of patient risk factors and fusions sites on union rates but found that primary studies did not report data in a way that would allow that analysis.

Randomized Controlled Trials

We found no RCTs comparing use of an orthobiologic to no orthobiologic. We did identify 2 RCTs, both non-inferiority studies, in patients undergoing hindfoot or ankle arthrodesis. In the first study, patients (n=434) requiring non-structural supplemental bone graft (<9 cc) as part of the arthrodesis procedure were randomized to receive either recombinant human platelet-derived growth factor-BB (rhPDGF-BB) homodimer combined with beta-tricalcium phosphate (β-TCP) or autograft.[16] The autografts were harvested from separate surgical sites. CT-confirmed fusion rates at 24 weeks post-surgery, the primary effectiveness outcome, were similar for the 2 groups. The groups were also comparable on other clinical outcomes including function and quality of life. There was less pain and fewer adverse events in the rhPDGF-BB/β-TCP group. The second study evaluated an injectable form of rhPDGF-BB/β-TCP.[15] In this study, 75 patients were randomized in a 5:1 ratio to rhPDGF-BB/β-TCP or autograft. An additional 142 patients who received autografts in the earlier RCT[16] were included as historical controls. The primary outcome (CT-confirmed fusion at 24 weeks) was similar for the 2 groups. Mean time to fusion was shorter in the rhPDGF-BB/β-TCP group. Non-inferiority was also demonstrated for pain, function, quality of life, and safety measures.

Donor Site Morbidity

A commonly cited concern with bone graft harvesting is donor site morbidity including infection, prolonged wound drainage, sensory loss, and pain.[13] Only one of our included studies reported a measure of donor site morbidity. Several case series, without a no-orthobiologic comparator, have assessed morbidity associated with graft harvest. In a retrospective study from the US, DeOrio and Farber included data from 180 patients with an iliac crest bone graft harvest procedure for foot and ankle surgery.[42] From the medical records, there were no major complications and 17 (9.5%) with minor complications – 12 with hematoma or seroma, 3 with lateral femoral cutaneous nerve irritation, 1 partial wound dehiscence, and 1 superficial wound infection. No extra hospital days were required, and no deep infections were reported. At a mean follow-up of 6 years (range 1 to 13), 134 of 169 (79%) of patients were able to be contacted. Of the 134 contacted, 120 (90%) reported no pain at the graft site. Among the 120 patients, 57% reported greater postoperative pain at the foot or ankle surgical site than at the harvest site; 27% reported greater postoperative pain at the harvest site than at the foot or ankle surgical site; and 16% reported that the postoperative pain was equal at the 2 sites.

A retrospective study from the United Kingdom focused on proximal tibia grafts for 148 foot and ankle arthrodesis procedures in 131 patients.[43] The mean time from surgery was 28 months (range 3 to 69 months). On a scale of 1 (no pain) to 5 (severe pain), the mean pain level post-surgery was 1.25. At follow-up, the mean was 1.04. No patient reported moderate or severe pain at any time. Four reported mild pain and 29 reported very mild pain initially with none reporting mild pain and 6 reporting very mild pain at follow-up. Post-operative paresthesia was reported in 8 patients (5.4%) with 4 resolved at follow-up. The single case of early superficial wound infection also resolved. There were no reported cases of hematoma or fracture.

Patients in the autograft group from the RCT comparing rhPDGF-BB/β-TCP to autograft[16] were assessed for harvest site pain during study follow-up.[44] The harvest site was selected by the study surgeons with 13% iliac crest, 51% proximal tibia, 18% distal tibia, and 15% calcaneus. Pain was assessed on a 100-point visual analog scale (VAS) with scores of 20 or higher indicating clinically significant pain. Post-surgery, the mean pain score was 32.9 with 49 patients (35.8%) reporting clinically significant pain at the harvest site. At 52 weeks, the mean score was 6.1 with 11 patients (8.5%) reporting clinically significant pain. The percentage of patients reporting clinically significant pain at 52 weeks was 0% for the iliac crest site, 13% for the distal tibia, 6% for the proximal tibia, and 20% for the calcaneus.

LIMITATIONS

In addition to limitations related to study design and sample size listed above, there are several other limitations of the available evidence.

1) The majority of studies assessed union rates using radiographs alone. In a previous case series, poor agreement was reported when radiographs and CT scans were used to determine the percentage of fusion following hindfoot arthrodesis involving the subtalar or a combination of the subtalar, talonavicular, and calcaneocuboid joints.[3] Assessments based on standard radiographs generally overestimated the degree of joint fusion in comparison to assessments based on the CT scans.

2) Few studies reported patient-centered outcomes such as pain, function, quality of life, or need for reoperation.

3) No studies reported costs. For autograft, costs will vary depending on the harvest site. A second surgical procedure, possibly involving a second surgeon, will likely increase operating room time and related costs. For manufactured products, costs vary, with higher costs for products containing living cells (*eg*, allograft with stem cells) and lower cost for bone products such as DBM. Cost also varies depending on the volume of product needed.

APPLICABILITY OF FINDINGS TO THE VA POPULATION

None of the included studies was conducted specifically with a VA population. Eleven of the 21 studies were from the US. Overall the mean age of patients included in the studies was 50 years with 55% male.

Based on the current state of evidence, we suggest consideration of utilization review and approval prior to use. This would focus orthobiologic use and a potential second surgical procedure on patients and/or arthrodesis sites of greatest risk for nonunion. Providers and policy makers should be aware of the cost and possible morbidity associated with widespread use of

orthobiologics given the insufficient to low-strength evidence of benefit – in particular, mostly radiographic rather than clinical outcomes. Furthermore, clinicians and patients should be aware that orthobiologic products are not specifically approved for use in foot and ankle arthrodesis. Thus, the clinical effectiveness, harms, and costs for foot and ankle arthrodesis are not well known and use of these products for these indications is considered "off label".

RESEARCH GAPS/FUTURE RESEARCH

Existing studies for the comparison of an orthobiologic to no orthobiologic are largely retrospective chart reviews. Few of the identified risk factors for nonunion (*eg,* smoking status, diabetes) were captured in the chart reviews. Selection bias, with surgeons electing to use an orthobiologic for more complex cases (*eg,* bone defects, high risk for nonunion), is also a concern.[1,5] There is limited evidence on specific indications for orthobiologic use during arthrodesis. Additionally, there is little information on cost of the products and cost/morbidity including donor site morbidity if autografts are used.

Future research should include standardized methods for processing and preparation of orthobiologics to allow for comparisons between studies. Outcome assessment should be standardized including protocols for capturing radiographic or CT images and measures of what constitutes fusion. Patient-centered outcomes should be captured and studies should include longer-term monitoring to capture adverse events.[11]

CONCLUSIONS

The available evidence is of poor quality due to study designs with high potential for selection bias; small sample sizes; inadequate reporting of patient and surgical risk factors for nonunion; and variations in populations studied, orthobiologics and surgical techniques used, and outcome assessment. As a result, there is very little evidence to inform surgeons regarding which patients might benefit most from orthobiologics or which orthobiologic to use. The absence of evidence that use of orthobiologics is superior to no orthobiologics suggests that a careful assessment of individual patient risk for nonunion is critical prior to orthobiologic use and that patients and clinicians should be informed that use of orthobiologics for foot and ankle arthrodesis is considered "off-label".

REFERENCES

1. Baumhauer JF, Pinzur MS, Daniels TR, et al. Survey on the need for bone graft in foot and ankle fusion surgery. *Foot Ankle Int.* 2013;34(12):1629-1633.
2. Lareau CR, Deren ME, Fantry A, Donahue RM, DiGiovanni CW. Does autogenous bone graft work? A logistic regression analysis of data from 159 papers in the foot and ankle literature. *Foot Ankle Surg.* 2015;21(3):150-159.
3. 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):780-787.
4. Krause F, Younger AS, Baumhauer JF, et al. Clinical outcomes of nonunions of hindfoot and ankle fusions. *J Bone Joint Surg Am.* 2016;98(23):2006-2016.
5. Yeoh JC, Taylor BA. Osseous healing in foot and ankle surgery with autograft, allograft, and other orthobiologics. *Orthop Clin North Am.* 2017;48(3):359-369.
6. Wallace GF. Current Orthobiologics for elective arthrodesis and nonunions of the foot and ankle. *Clin Podiatr Med Surg.* 2017;34(3):399-408.
7. DiGiovanni CW, Lin SS, Daniels TR, et al. The importance of sufficient graft material in achieving foot or ankle fusion. *J Bone Joint Surg Am.* 2016;98(15):1260-1267.
8. Thevendran G, Shah K, Pinney SJ, Younger AS. Perceived risk factors for nonunion following foot and ankle arthrodesis. *J Orthop Surg.* 2017;25(1):2309499017692703.
9. Thevendran G, Younger A, Pinney S. Current concepts review: risk factors for nonunions in foot and ankle arthrodeses. *Foot Ankle Int.* 2012;33(11):1031-1040.
10. DiDomenico LA, Thomas ZM. Osteobiologics in foot and ankle surgery. *Clin Podiatr Med Surg.* 2015;32(1):1-19.
11. West TA, Williams ML. Orthobiologics. *Clin Podiatr Med Surg.* 2019;36(4):609-626.
12. American Academy of Orthopaedic Surgeons. Helping Fractures Heal (Orthobiologics). OrthoInfo Web site. https://orthoinfo.aaos.org/en/treatment/helping-fractures-heal-orthobiologics/. Published 2010. Accessed 17 November 2019.
13. 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):112-120.
14. Lin SS, Montemurro NJ, Krell ES. Orthobiologics in Foot and Ankle Surgery. *J Am Acad Orthop Surg.* 2016;24(2):113-122.
15. Daniels TR, Younger AS, Penner MJ, et al. Prospective randomized controlled trial of hindfoot and ankle fusions treated with rhPDGF-BB in combination with a beta-TCP-collagen matrix. *Foot Ankle Int.* 2015;36(7):739-748.
16. DiGiovanni CW, Lin SS, Baumhauer JF, et al. Recombinant human platelet-derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/beta-TCP): an alternative to autogenous bone graft. *J Bone Joint Surg Am.* 2013;95(13):1184-1192.

17. Harford JS, Dekker TJ, Adams SB. Bone marrow aspirate concentrate for bone healing in foot and anklesurgery. *Foot Ankle Clin.* 2016;21(4):839-845.

18. Tufanaru C MZ, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E MZ, ed. *Joanna Briggs Institute Reviewer's Manual*: The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/ (Accessed October 2, 2019)

19. Moola S MZ, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E MZ, ed. *Joanna Briggs Institute Reviewer's Manual*: The Joanna Briggs Institute; 2017. Available from https://reviewersmanual.joannabriggs.org/ (Accessed October 2, 2019)

20. Abd-Ella MM, Galhoum A, Abdelrahman AF, Walther M. Management of nonunited talar fractures with avascular necrosis by resection of necrotic bone, bone grafting, and fusion with an intramedullary nail. *Foot Ankle Int.* 2017;38(8):879-884.

21. Anderson J, Jeppesen N, Hansen M, Brady C, Gough A, Fowler Z. First metatarsophalangeal joint arthrodesis: comparison of mesenchymal stem cell allograft versus autogenous bone graft fusion rates. *Surgical Science.* 2013;4:263-267.

22. Bibbo C, Patel DV, Haskell MD. Recombinant bone morphogenetic protein-2 (rhBMP-2) in high-risk ankle and hindfoot fusions. *Foot Ankle Int.* 2009;30(7):597-603.

23. Buda M, Hagemeijer NC, Kink S, Johnson AH, Guss D, DiGiovanni CW. Effect of fixation type and bone graft on tarsometatarsal fusion. *Foot Ankle Int.* 2018;39(12):1394-1402.

24. Cao HH, Lu WZ, Tang KL. Isolated talonavicular arthrodesis and talonavicular-cuneiform arthrodesis for the Muller-Weiss disease. *J Orthop Surg Res.* 2017;12(1):83.

25. Chahal J, Stephen DJ, Bulmer B, Daniels T, Kreder HJ. Factors associated with outcome after subtalar arthrodesis. *J Orthop Trauma.* 2006;20(8):555-561.

26. Chen YJ, Huang TJ, Shih HN, Hsu KY, Hsu RW. Ankle arthrodesis with cross screw fixation. Good results in 36/40 cases followed 3-7 years. *Acta Orthop Scand.* 1996;67(5):473-478.

27. Easley ME, Trnka HJ, Schon LC, Myerson MS. Isolated subtalar arthrodesis. *J Bone Joint Surg Am.* 2000;82(5):613-624.

28. Fourman MS, Borst EW, Bogner E, Rozbruch SR, Fragomen AT. Recombinant human BMP-2 increases the incidence and rate of healing in complex ankle arthrodesis. *Clin Orthop Relat Res.* 2014;472(2):732-739.

29. Grunander TR, Thordarson DB. Results of calcaneocuboid distraction arthrodesis. *Foot Ankle Surg.* 2012;18(1):15-18.

30. Holm JL, Laxson SE, Schuberth JM. Primary subtalar joint arthrodesis for comminuted fractures of the calcaneus. *J Foot Ankle Surg.* 2015;54(1):61-65.

31. Lechler P, Graf S, Kock FX, Schaumberger J, Grifka J, Handel M. Arthrodisis of the talonavicular joint using angle-stable mini-plates: a prospective study. *Int Ortho.* 2012;36:2491-2494.

32. Patil S, Auyeung J, Gower A. Outcome of subtalar fusion using bovine cancellous bone graft: a retrospective case series. *J Foot Ankle Surg.* 2011;50(4):388-390.

33. Plaass C, Knupp M, Barg A, Hintermann B. Anterior double plating for rigid fixation of isolated tibiotalar arthrodesis. *Foot Ankle Int.* 2009;30(7):631-639.

34. Rearick T, Charlton TP, Thordarson D. Effectiveness and complications associated with recombinant human bone morphogenetic protein-2 augmentation of foot and ankle fusions and fracture nonunions. *Foot Ankle Int.* 2014;35(8):783-788.

35. Rungprai C, Phisitkul P, Femino JE, Martin KD, Saltzman CL, Amendola A. Outcomes and complications after open versus posterior arthroscopic subtalar arthrodesis in 121 patients. *J Bone Joint Surg Am.* 2016;98(8):636-646.

36. Sun L, Kong Z, Xu M. Minimally invasive subtalar arthrodesis for traumatic subtalar arthritis. *J Int Med Res.* 2019;47(12):6129-6138.

37. Weinraub GM, Schuberth JM, Lee M, et al. Isolated medial incisional approach to subtalar and talonavicular arthrodesis. *J Foot Ankle Surg.* 2010;49(4):326-330.

38. Wheeler J, Sangeorzan A, Crass SM, Sangeorzan BJ, Benirschke SK, Hansen ST. Locally generated bone slurry accelerated ankle arthrodesis. *Foot Ankle Int.* 2009;30(7):686-689.

39. Yavuz U, Sokucu S, Demir B, Ozer D, Ozcan C, Kabukcuoglu YS. Isolated subtalar fusion for neglected painful intra-articular calcaneal fractures. *Acta Orthop Traumatol Turc.* 2014;48(5):541-545.

40. Yildirim T, Sofu H, Camurcu Y, Ozcan C, Oner A, Sahin V. Isolated subtalar arthrodesis. *Acta Orthop Belg.* 2015;81(1):155-160.

41. Muller MA, Frank A, Briel M, et al. Substitutes of structural and non-structural autologous bone grafts in hindfoot arthrodeses and osteotomies: a systematic review. *BMC Musculoskelet Disord.* 2013;14:59.

42. DeOrio JK, Farber DC. Morbidity associated with anterior iliac crest bone grafting in foot and ankle surgery. *Foot Ankle Int.* 2006;25(2):147-151.

43. Whitehouse MR, Lankester BJ, Winson IG, Hepple S. Bone graft harvest from the proximal tibia in foot and ankle arthrodesis surgery. *Foot Ankle Int.* 2006;27(11):913-916.

44. Baumhauer J, Pinzur MS, Donahue R, Beasley W, DiGiovanni C. Site selection and pain outcome after autologous bone graft harvest. *Foot Ankle Int.* 2014;35(2):104-107.