
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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U.S. Department of Veterans Affairs

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
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Section Chief, Podiatry – Surgical Service
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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.

EXECUTIVE SUMMARY

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. However, reported rates of nonunion following foot and ankle arthrodesis range from 0 to 36% with an average of 10 to 11%.

Nonunion following arthrodesis surgery is associated with poor function, disability, and the potential need for revision surgery. A number of factors have been reported to be associated with nonunion including patient factors, local factors at the site of surgery, and surgical factors.

Orthobiologics are biologically derived materials that may be used, in the context of arthrodesis, to promote bone formation and union at the arthrodesis site. 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, osteoinduction, and osteogenesis.

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.

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]). Concerns with manufactured products include variability in manufacturing and differences across products in the same class due to proprietary preparation methods.

The purpose of our review was to examine the evidence from studies comparing use of an orthobiologic 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?

METHODS

Data Sources and Searches

We searched Ovid MEDLINE, Embase, and the Cochrane Library from 1995 to July 2019 using Medical Subject Headings (MeSH) and title/abstract words for orthobiologics. 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 and Quality Assessment

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.

We used elements from the Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies and Critical Appraisal Checklist for Case Series 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.

RESULTS

Results of Literature Search

Our literature search 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 and included 21.

Summary of Results for Key Question 1

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. 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.

Summary of Results for Key Question 2

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.

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 to 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.

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 joint or a combination of the subtalar, talonavicular, and calcaneocuboid joints. 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.

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”. 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 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.

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. There is limited evidence on specific indications for orthobiologic use during arthrodesis.

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.

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.

ABBREVIATIONS TABLE

Abbreviation	Definition
BMA/BMAC	Bone marrow aspirate/bone marrow aspirate concentrate
BMP	Bone morphogenic protein
CT	Computed tomography
DBM	Demineralized bone matrix
FDA	Food and Drug Administration
PDGF	Platelet-derived growth factor
PRP	Platelet-rich plasma
RCT	Randomized controlled trial
SC	Stem cells
VA	Veterans Affairs