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## Recombinant human platelet-derived growth factor-BB versus autologous bone graft in foot and ankle fusion: A systematic review and meta-analysis

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### ABSTRACT

Today, autogenous bone graft (ABG) is still considered as the gold standard for joint fusion. Recombinant human platelet-derived growth factor-BB (rhPDGF-BB) which is of chemotactic and mitogenic to mesenchymal stem cells and possesses outstanding osteogenic potentials has been used for ankle and foot fusion in recent years. The goal of this article is to evaluate the safety and efficacy of rhPDGF-BB versus ABG in foot and ankle fusion. The PubMed MEDLINE, EMBASE, Web of Science, and Cochrane Library were systematically searched. Finally, three randomized controlled trials (RCTs) with 634 patients were enrolled in this study. Results of radiologic effectiveness which included CT and radiographic union rates revealed that there was no significant difference between rhPDGF-BB approach and ABG approach. Analysis of clinical results held the same outcomes expect that ABG group was superior in long-term Short Form-12 physical component scores. The pooled results also demonstrated that rhPDGF-BB was as safe as ABG in foot and ankle surgery. However, autograft harvesting procedure has some drawbacks such as donor-site pain and morbidity, additional operation time, blood loss, and scarring, which can be overcome by rhPDGF-BB. Thus, rhPDGF-BB is a viable alternative to autograft in foot and ankle fusion surgery. Yet, more high-quality RCTs with long-term follow-up are still required to make the final conclusion.

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## 1. Background

The arthritis of ankle and foot joints usually result in pain, deformity and functional limitation, which significantly influence quality of life [1]. Today, arthrodesis is still a common and reliable surgical treatment option for end-stage of ankle and foot arthritis. However, the ankle and foot joints bear the highest loads per square centimeter in whole body [2], which makes them prone for complications when fused. One of the most common complications

is nonunion. As the nonunion rate of this procedure could be 15–40% [3] with an overall rate of 10% [4], bone grafts have been used to promote bony union [5,6].

Autogenous bone graft (ABG) is currently considered as the gold standard for its outstanding osteoinductivity and osteoconductivity [7]. However, this kind of bone graft possesses the deficiency of deep infection, limited resource, chronic pain, and donor site morbidity [4,8]. It takes additional operative time as well [9]. These limitations indicate a clear need for a novel graft production which can avoid weaknesses of ABG while holding equal fusion capacity.

The platelet-derived growth factor (PDGF) which contains 5 kinds of homodimers (AA, AB, BB, CC, and DD) is primarily secreted from platelet  $\alpha$ -granules [9,10]. PDGF can stimulate new tissue repair through its role of mitogen and chemotactic agent for cells of mesenchymal origin [11,12]. Among these homodimers, PDGF-BB is considered to be the most active PDGF isoform in bone and other

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connective tissue as it can bind to all known PDGF receptors [13,14]. The security of PDGF-BB has also been demonstrated [15].

For aforementioned advantages, recombinant human PDGF-BB (rhPDGF-BB) combined with  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) has been used for ankle and foot fusion in recent years. Most outcomes of previous studies revealed that rhPDGF-BB approach and ABG approach were comparable [16–18]. However, the sample size enrolled in each study was relatively small, which may influence quality of the evidence. So, we conduct this meta-analysis to make a relatively more credible and overall assessment about rhPDGF-BB versus ABG in ankle and foot fusion.

## 2. Materials and methods

### 2.1. Search strategy and study selection

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [19] and the recommendations of Cochrane Collaboration [20] were followed to carry out this meta-analysis. The PubMed MEDLINE, EMBASE, Web of Science, and Cochrane Library were searched for randomized controlled trials published up to July 2015. Key terms used for database research were: autologous bone graft, platelet derived growth factor, ankle, foot, fusion, and arthrodesis. Boolean operators of “OR” and “AND” were used to combine the literature searches. We also manually searched the references of full-text articles to avoid omitted studies. No restriction of publication language was applied.

Studies were included if the study was a randomized controlled trial (RCT) focusing on comparing rhPDGF-BB versus ABG in foot and ankle fusion. One of the following results should have been reported: CT fusion rates, radiographic union rates, clinical success rates, fusion site visual analog scale (VAS) scores, American Orthopaedic Foot & Ankle Society (AOFAS) scores, foot function index scores, Short Form-12 (SF-12) physical component scores, clinical healing status (patient level), therapeutic failure rates, weight-bearing pain, device-related treatment emergent adverse events, complications associated with surgical procedure, serious operative complications, serious treatment emergent adverse events, or serious operative wound infections. Retrospective studies, non-randomized controlled trials, reviews, and basic researches were excluded.

Titles and abstracts related to the eligibility criteria were screened independently by two independent authors. We also read full-text of the primarily screened literature to make the final inclusion. All reviewers followed the unified search strategy. Any disagreement was resolved by discussion.

### 2.2. Data extraction

Two reviewers extracted the data. Discrepancies about data extraction were resolved by discussion among the first three authors. Relevant parameters included patient characteristics (e.g. age, sex), duration of follow-up, intervention and outcomes. The primary outcome measures were CT fusion rates and radiographic union rates, and the secondary outcomes included clinical success rate, fusion site VAS scores, AOFAS scores, foot function index scores, SF-12 physical component scores, clinical healing status (patient level), therapeutic failure rate, weight-bearing pain, device-related treatment emergent adverse events, complications associated with surgical procedure, serious operative complications, serious treatment emergent adverse events, and serious operative wound infections. We defined ‘mid-term’ as 4 weeks to 6 months, and ‘long-term’ was more than 6 months.

### 2.3. Data analysis

Review Manager Software (RevMan Version 5.3, The Cochrane Collaboration, Copenhagen, Denmark) was used to performed this meta-analysis. Risk ratios (RR) and 95% confidence intervals (CI) were used for dichotomous outcomes while mean difference (MD) and 95% CI were used to assess continuous outcomes. The  $p$  value less than 0.05 was regarded as statistically significant. We used the  $Q$  test and  $I^2$  statistic to evaluate heterogeneity. A random effect model was used if  $p < 0.1$  and  $I^2 > 50\%$  which indicated heterogeneity. On the contrary, a fixed effects model was used when  $p \geq 0.1$  and  $I^2 \leq 50\%$ . If there was a conflict between  $Q$  test and  $I^2$  statistic, we judged the heterogeneity according to the result of  $Q$  test. Sensitivity analysis was used to investigate the source of heterogeneity.

### 2.4. Assessment of methodological quality and evidence synthesis

The risk of bias in the included studies was evaluated by two reviewers. The assessment was based on the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [21] applying “Cochrane collaboration’s tool for assessing the risk of bias”. We also evaluated evidence grade of outcome according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [22]. Any disagreement was unified by discussing with a third reviewer.

## 3. Results

### 3.1. Search results

461 studies were found through the primary search. Then, 35 studies were assessed for eligibility and full-text read after excluding duplicate and irrelevant studies. Among them, the following 32 studies were excluded: 3 basic researches, 9 review articles, 7 studies in which the grafts were not applied in foot or ankle fusion, and 13 studies that did not include comparison between rhPDGF-BB and ABG. Finally, 3 prospective RCTs studies were finally enrolled in our study [16–18] (Fig. 1).

A total of 634 patients (337 in rhPDGF-BB group and 297 in ABG group) with mean age of 56.59 years old were enrolled in this meta-analysis. Among them, 300 were female patients and 334 were male patients. These patients were followed up for an average of 51.50 weeks. All the 3 studies used a combination of rhPDGF-BB (0.3 mg/ml) and  $\beta$ -TCP as bone graft for foot and ankle fusion. Detailed characteristics are summarized in Table 1.

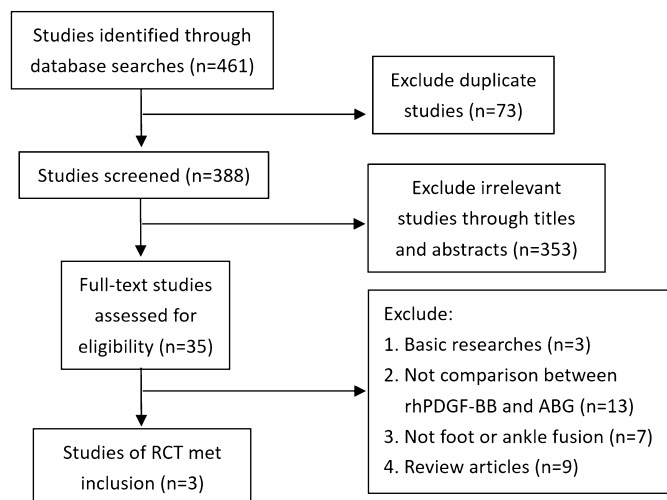


Fig. 1. Flow chart of study selection process.

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