

Growth factors for treating diabetic foot ulcers

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Resumen

Background

Foot ulcers are a major complication of diabetes mellitus, often leading to amputation. Growth factors derived from blood platelets, endothelium, or macrophages could potentially be an important treatment for these wounds but they may also confer risks.

Objectives

To assess the benefits and harms of growth factors for foot ulcers in patients with type 1 or type 2 diabetes mellitus.

Search methods

In March 2015 we searched the Cochrane Wounds Group Specialised Register, The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), Ovid MEDLINE, Ovid MEDLINE (In-Process & Other Non-Indexed Citations, Ovid EMBASE and EBSCO CINAHL. There were no restrictions with respect to language, date of publication or study setting.

Selection criteria

Randomised clinical trials in any setting, recruiting people with type 1 or type 2 diabetes mellitus diagnosed with a foot ulcer. Trials were eligible for inclusion if they compared a growth factor plus standard care (e.g., antibiotic therapy, debridement, wound dressings) versus placebo or no growth factor plus standard care, or compared different growth factors against each other. We considered lower limb amputation (minimum of one toe), complete healing of the foot ulcer, and time to complete healing of the diabetic foot ulcer as the primary outcomes.

Data collection and analysis

Independently, we selected randomised clinical trials, assessed risk of bias, and extracted data in duplicate. We estimated risk ratios (RR) for dichotomous outcomes. We measured statistical

heterogeneity using the I² statistic. We subjected our analyses to both fixed-effect and random-effects model analyses.

Main results

We identified 28 randomised clinical trials involving 2365 participants. The cause of foot ulcer (neurologic, vascular, or combined) was poorly defined in all trials. The trials were conducted in ten countries. The trials assessed 11 growth factors in 30 comparisons: platelet-derived wound healing formula, autologous growth factor, allogeneic platelet-derived growth factor, transforming growth factor beta 2, arginine-glycine-aspartic acid peptide matrix, recombinant human platelet-derived growth factor (becaplermin), recombinant human epidermal growth factor, recombinant human basic fibroblast growth factor, recombinant human vascular endothelial growth factor, recombinant human lactoferrin, and recombinant human acidic fibroblast growth factor. Topical intervention was the most frequent route of administration. All the trials were underpowered and had a high risk of bias. Pharmaceutical industry sponsored 50% of the trials.

Any growth factor compared with placebo or no growth factor increased the number of participants with complete wound healing (345/657 (52.51%) versus 167/482 (34.64%); RR 1.51, 95% CI 1.31 to 1.73; I² = 51%, 12 trials; low quality evidence). The result is mainly based on platelet-derived wound healing formula (36/56 (64.28%) versus 7/27 (25.92%); RR 2.45, 95% 1.27 to 4.74; I² = 0%, two trials), and recombinant human platelet-derived growth factor (becaplermin) (205/428 (47.89%) versus 109/335 (32.53%); RR 1.47, 95% CI 1.23 to 1.76, I² = 74%, five trials).

In terms of lower limb amputation (minimum of one toe), there was no clear evidence of a difference between any growth factor and placebo or no growth factor (19/150 (12.66%) versus 12/69 (17.39%); RR 0.74, 95% CI 0.39 to 1.39; I² = 0%, two trials; very low quality evidence). One trial involving 55 participants showed no clear evidence of a difference between recombinant human vascular endothelial growth factor and placebo in terms of ulcer-free days following treatment for diabetic foot ulcers (RR 0.64, 95% CI 0.14 to 2.94; P value 0.56, low quality of evidence)

Although 11 trials reported time to complete healing of the foot ulcers in people with diabetes, meta-analysis was not possible for this outcome due to the unique comparisons within each trial, failure to report data, and high number of withdrawals. Data on quality of life were not reported. Growth factors showed an increasing risk of overall adverse event rate compared with compared with placebo or no growth factor (255/498 (51.20%) versus 169/332 (50.90%); RR 0.83; 95% CI 0.72 to 0.96; I² = 48%; eight trials; low quality evidence). Overall, safety data were poorly reported and adverse events may have been underestimated.

Authors' conclusions

This Cochrane systematic review analysed a heterogeneous group of trials that assessed 11 different growth factors for diabetic foot ulcers. We found evidence suggesting that growth factors may increase the likelihood that people will have complete healing of foot ulcers in people with diabetes. However, this conclusion is based on randomised clinical trials with high risk of systematic errors (bias). Assessment of the quality of the available evidence (GRADE) showed that further trials investigating the effect of growth factors are needed before firm conclusions can be drawn. The safety profiles of the growth factors are unclear. Future trials should be conducted according to SPIRIT statement and reported according to the CONSORT statement by independent investigators and using the Foundation of Patient-Centered Outcomes Research recommendations.

Palabras clave

KeyWords Plus: QUALITY-OF-LIFE; LOWER-EXTREMITY AMPUTATIONS; PLATELET-RICH PLASMA; RANDOMIZED CONTROLLED-TRIALS; INTERNATIONAL-WORKING-GROUP; CENTERED OUTCOMES RESEARCH; FACTOR-BB BECAPLERMIN; RISK-FACTORS; DOUBLE-BLIND; CLASSIFICATION-SYSTEM