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Review

Management and outcome of diaphyseal aseptic non-unions of the lower limb: A systematic review

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ABSTRACT

Objectives: To review current treatments utilising biological enhancement modalities and their efficacy for the management of lower limb long bone aseptic non-unions.
Materials & methods: A systematic review of English articles using PubMed Medline; Ovid Medline; Embase; and the Cochrane Library was performed, supplemented by a manual search of bibliographies.
Results: Thirteen manuscripts met the inclusion criteria reporting on 428 patients. The overall healing had a pooled estimate of effect size at 94.3%. The calculated summarised estimate of effect size for deep infection rate (413 patients) was 2.3%. Three subgroups were then created on the basis of the exact type of graft used at the non-union site (ABG, BMP-7, BMP-7 + ABG). Comparison between the above subgroups revealed that ABG resulted in approximately 3-fold increase of the odds of healing compared with the use of BMP-7. Combined use of ABGs and BMP-7 improved the odds of healing by 3.5 times compared with BMP-7 alone. However, the previous median operations prior to the implantation of ABG or BMP-7 treatment was 1.09 versus 2.3 respectively ($p = 0.02$). Although the implantation of ABG was associated with a greater incidence of infection the documented differences did not reach significance.
Conclusions: Although ABG was found to have a higher success rate compared to BMP-7 (95% Vs 87%), patients treated with BMP-7 had a higher number of previous failed interventions, statistically significantly so (BMP-7 is used for the treatment of more recalcitrant non-unions). It is the surgeon's judgement that should determine the most suitable treatment modality, depending on the nature and characteristics (personality) of the non-union and the patient.

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Introduction

Bone healing and bone regeneration represents a complex, well-orchestrated physiological process, margined by the combination of osteoconduction (the formation of a scaffold for the bone to grow into), osteoinduction (promoted by cell migration, inflammatory cytokines and growth factors) and osteogenesis (the formation of new bone by osteoprogenitor cells).[1,2] Any inhibition to one or more of these steps can lead to failure of healing and a non-union.

Still, the criteria for defining a non-union are not standardised and the assessment of fracture healing varies considerably between the orthopaedic surgeons.[3] The FDA defines non-union as incomplete fracture healing within nine months following injury along with no progression towards healing on serial radiographs over the course of three consecutive months.[4] Among all fractures, it has been estimated that 2–5% are complicated with delayed or non-union.[5] Tibia is the most frequently involved long bone with a prevalence of non-union ranging from 1.1% to 19%,[6,7] whereas the incidence of femoral shaft non-union can reach as high as 12.5%.[8,9]

Various risk factors have been implicated with compromised fracture healing. They are generally divided into patient dependent factors such as medical comorbidities, age, gender, smoking and anti-inflammatory use; and patient independent factors that may include the personality of the fracture, the quality of surgical management and the presence of infection.[4,10] In general, the cause of non-union is multifactorial,[11] although in many cases no identifiable cause for the impaired healing can be isolated.

Lower limb long bone non-unions represent an international public health problem and an economic burden to the healthcare system.[12] Their consequences can be devastating for the patient, his family and thereafter the society as a whole. Prolonged disability, consecutive re-operations and long abstinence from work pose a heavy psychological burden and an impaired quality of life.[13]

Due to the heterogeneity of long bone non-unions, their treatment can be complex and challenging. According to their radiologic and histologic appearance, non-unions can be classified as hypertrophic (decreased mechanical stability and callus formation) or atrophic (little callus formation around a fibrous tissue-filled fracture gap).[14,15] For a successful outcome, understanding of the biological process of fracture healing is required whereas treatment should be tailored to each individual addressing all components of the problem.

With regards to the biological stimulation, in addition to the use of autologous bone grafting usually harvested from the iliac crest, the so-called "gold standard",[16] other materials that have been used include allograft, xenograft (bovine cancellous chips), synthetic bone graft, bone morphogenetic proteins (BMPs), platelet rich plasma (PRP), mesenchymal stem cells (MSC's) or combinations of the above.

The purpose of this study is to review current treatments utilising biological enhancement modalities and their efficacy for the management of aseptic non-unions of lower limb long bones, in skeletally mature patients.

Methods and materials

The review was conducted in accordance to the PRISMA guidelines.[17] A protocol was utilised for the documentation of the data, where objectives, methods of analysis and inclusion criteria were specified in detail.

Our primary objective was to document and compare the healing rates of lower limb long bone non-unions (femur–tibia), treated with various modalities (autologous bone grafts or bone graft substitutes). The secondary outcome measure was to check for any potential complications related to each of the treatment methods used.

Eligibility criteria

Studies selected were original articles that fulfilled the following inclusion criteria: (1) biological enhancement studies (bone grafting, application of BMPs, platelet rich plasma (PRP), mesenchymal stem cells or combinations of the above) that enrolled skeletally mature patients with aseptic non-unions of the lower limb; (2) the non-union involved the diaphysis (shaft) of the bone; (3) ten or more patients were included for each treatment modality; (4) follow-up was for at least six months after the index procedure, and after clinical and radiological union had occurred; (5) articles were published in English language; and (6) the full text of each article was available. Exclusion criteria: (1) patients with bone defects/bone gap >2.5 cm or patients for whom a lengthening procedure was deemed necessary; (2) non-unions as a result of tumour excision, radiation or following elective osteotomies; (3) non-unions complicating peri-prosthetic fractures; (4) non-unions treated with vascularised grafts; and (5) animal studies.

Information sources

Studies were identified by searching the PubMed Medline; Ovid Medline; Embase; and the Cochrane Library, to retrieve all available relevant articles, using the terms non-union, aseptic, diaphyseal, shaft, femur, tibia, long bones, bone graft, bone morphogenic proteins (BMPs), mesenchymal stem cells (MSCs) and platelet rich plasma (PRP). The bibliographies of identified articles, including relevant reviews and meta-analyses were manually searched for potential eligible reports. In case of missing information in a study, an attempt was made to acquire those from the investigators. Only articles written in English language were investigated during search process, whereas no publication date restrictions were imposed.

Study selection

Eligibility assessment was performed independently in an unblinded standardised manner by two of the authors (M.P., S.P.). Most citations could be excluded on the basis of information provided by their respective title or abstract. Otherwise, the complete manuscript was obtained and carefully scrutinised by the two reviewers. Any disagreement between reviewers was resolved by consensus.