Injury, Int. J. Care Injured 44 (2013) S1, S34–S39

Contents lists available at SciVerse ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Clinical applications of growth factors in bone injuries: Experience with BMPs

Mario Ronga *, Alessandro Fagetti, Gianluca Canton, Elia Paiusco, Michele Francesco Surace, Paolo Cherubino

Department of Biotechnology and Life Sciences (DBSV), University of Insubria, Varese, Italy

ARTICLE INFO

Keywords:
Bone morphogenetic protein (BMP)
Fracture healing
Open fracture
Non-union

ABSTRACT

The management of open fractures and delayed or non unions continue to be complicated by high rates of treatment failure and significant patient disability and dissatisfaction. The use of bone morphogenetic proteins (BMPs) in the treatment of these injuries has been assessed by several authors. BMPs induce the process of bone healing by recruiting bone-forming cells to the area of lesion. The use of BMP currently has two FDA-approved indications: treatment of open tibial fractures treated with intramedullary fixation and treatment of tibia long bone non-union. Despite this limited target, off-label BMP use continues to push the spectrum for new applications. This review describes the current evidence for the use of BMPs in open fractures and non-unions.

Introduction

The prevalence of non-union has been estimated to be approximately 10% of all fractures and this number raises to 50% for open tibia fractures.[1] This problem results in high costs for the health care system and for the patient inability to return to work and sports activities. In the United States the total cost for non-union management is about 14.6 million dollars per year.[2]

In the past, autograft, allograft and xenograft bone has been used as the basis for biological stimulation of non-unions.[3,4] Autograft has been considered the gold-standard bone graft in this type of surgery. Limitations of the use of autograft include its volume quantity and donor site morbidity; chronic pain has been reported in 18–24% of cases at 2 years.[5] Minor complications included superficial infections, and minor hematomas. Major complications included herniation of abdominal contents through massive bone graft donor sites, vascular injuries, deep infections, neurologic injuries, and iliac wing fractures.[6]

Several authors have pointed out that the concentration of growth factors and in particular of Bone Morphogenetic Proteins (BMPs) at the non-union site represents one of the key factors to successful treatment.[3,6,7] Nowadays it is possible to obtain high concentration of single growth factors such as BMPs due to the advances made in recombinant DNA technology.[7] Several *in vitro* and *in vivo* studies have demonstrated the efficacy of recombinant osteogenic protein (rhBMP) in bone regeneration.[8,9] In the literature several prospective randomized clinical trials (RCTs) and case series have been published on the use of rhBMP in different anatomical sites.[10–19,?]

The aim of this paper is to report a brief review on the use of rhBMP for bone regeneration in clinical practice.

Materials and methods

Two reviewers (AF and GC) independently identified studies by a systematic search of Embase, Medline, and the Cochrane Central Registry of Controlled Trials, from inception of the database to 28 February 2012, using various combinations of the keywords terms “recombinant”, “bone morphogenetic protein”, “BMP”, “human”, “open, fracture”, “non-union”, “trauma”, “cost-effectiveness”, “complication”. Aim of this review is to report a summary of success and failure rates of clinical application of BMPs in open fractures and non-unions. Inclusion criteria were: papers written in English, peer-reviewed journals, randomized controlled trials, prospective and retrospective case series. Exclusion criteria were: abstracts, case reports, reviews. For “complications” and “cost-effectiveness” sections case reports and reviews were included. The two reviewers screened the titles and abstracts of the citations identified independently and in duplicate, and acquired the full text of any article that either judged potentially eligible. These reviewers independently applied eligibility criteria to the methods section of potentially eligible trials. We resolved disagreements by discussion.

Results

A total of 22 studies were included in this review.[10–14,16–32] Four case reports or small case series describing complications related to the use of BMPs were also included.[33–36] Tables 1 and 2 summarize the success rate of BMPs in open fractures and non-unions.

* Corresponding author: Mario Ronga, MD, Department of Biotechnology and Life Sciences (DBSV), University of Insubria, Hospital di Circolo, Viale L. Borri 57, 21100 Varese, Italy. Tel.: +39 0332 278 824. Fax: +39 0332 278 825.
E-mail address: mario.ronga@uninsubria.it (M. Ronga).

0020-1383/$ – see front matter

Table 1
Success rate of BMPs in open fractures.

Authors	Anatomical site	BMP/graft*	Union rates
Govender et al., 2002[17]	tibia	– standard care IM nail (150) – standard care + 0.75 mg/mL BMP-2 (151) – standard care + 1.50 mg/mL BMP-2 (149)	– 47% – 54% – 65%
Jones et al., 2006[27]	tibia	– autogenous bone graft (15) – BMP-2 and cancellous allograft (15)	– 10/15 (66,6%) – 13/15 (86,6%)
Swiontkowki et al., 2006[20]	tibia	– standard treatment (131) – standard care + 1.50 mg/mL BMP-2 (113)	– 80% – 98%
Schwartz et al., 2006[31]	tibia	– BMP-2 in combination with bone graft substitute (calcium phosphate or calcium sulfate) (19)	– 84%
Ristiniemi et al., 2007[30]	tibia	– external Fixator (20) – external Fixator + BMP-7 (20)	– 18/20 (90%) – 13/20 (65%)
Kuklo et al., 2008[29]	tibia	– autogenous bone (67) – BMP-2 (62)	– 76% – 92%

*( ) shows the number of cases treated.

Table 2
Success rate of BMPs in non-unions.

Authors	Anatomical site	BMP/graft*	Union rates
Cook et al., 1999[21]	tibia	– BMP-7 (14) – autograft (16)	– 86% (12/14) – 94% (15/16)
Friedlaender et al., 2001[14]	tibia	– iliac crest bone (61) – BMP-7 (63)	– 84% – 75%
Bong et al., 2005[11]	humerus	– BMP-7 and bone grafts (23)	– 100%
Giannoudis et al., 2005[16]	different sites	– 395/653 non-unions	– 82%
Bilic et al., 2006[10]	scaphoid	– BMP-7 + autograft (6) – autologous iliac graft (6) – BMP-7 + allograft (5)	– 100%
Ronga et al., 2006[19]	different sites	– BMP-7 + autograft – BMP-7 alone or added to non-osteoinductive grafts	– 86% – 85.7%
Giannoudis et al., 2007[26]	pelvis	– BMP-7 (9)	– 8/9 (89%)
Desmyter et al., 2008[24]	tibia	– BMP-7 (62)	– 84.9%
Kanakaris et al., 2009[28]	femur	– BMP-7 (30)	– 86.6%
Kanakaris et al., 2008[18]	tibia	– BMP-7 (68)	– 89.7%
Calori et al., 2008[12]	tibia, femur, humerus, ulna, radius	– BMP group: 5 tibial, 10 femoral, 15 humeral, 12 ulnar, and 8 radial – PRP group: 19 tibial, 8 femoral, 16 humeral, 8 ulnar, and 9 radial	– rhBMP-7: 52 (86.7%) – PRP: 41 (68.3%)
Giannoudis et al., 2009[25]	humerus, femur, tibia	– BMP-7 and autologous bone graft (7 humerus, 19 femur, 19 tibia)	– 100%
Crawford et al., 2009[22]	humerus	– BMP-2 (9)	– 8/9 (88.8%)
Dohin et al., 2009[13]	long bones non-unions	– BMP-7 (23)	– 17/23 (73.9%)
Desai et al., 2010[23]	tibia	– autograft (RIA) + BMP-2 (9)	– 100%
Tressler at al., 2011[32]	different sites	– Group 1 (74): Autologous iliac crest bone graft – Group 2 (19): BMP-2 with allograft cancellous bone chips	– Group 1: 63/74 (85.1) – Group 2: 13/19 (68.4)

*( ) shows the number of cases treated.

Use in open fractures

The rationale for the use of BMPs in open fractures is based on the evidence of quicker bone formation and increase in angiogenesis at the fracture site, with consequent reduction of long term complications.[37,38] The BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) trial is a multicentre, prospective, randomized, controlled trial that included the largest number of patients (450) with tibia open fractures.[17] After initial debridement of the open fracture site and osteosynthesis with intramedullary nail, patients were randomized to receive either the standard of care or the addition of BMP-2. Randomization was stratified according to the Gustilo-Anderson classification,[39] in order to obtain an equal number of "type III fractures" for each group. Patients were followed for 12 months. A lower percentage of patients required further surgery in the BMP-2 group in comparison to the control group (26% vs. 46%, $p = 0.0004$). In the BMP-2 group a quicker bone callus formation and wound closure were observed. Subgroup analysis "type IIIA and IIIB open fractures" demonstrated a lower rate of infection in the BMP-2 group (24% vs 44%, $p = 0.0219$). Two major limitations can be raised to this study. The "single-blind" design: the surgeon knew which patients had received BMP-2 and therefore could have been bias in defining failures. The "BMP-2" group was treated with a higher number of reamed nails determining a potential bias. Swiontkowksi et al. have compared a subgroup of the BESTT trial patients with a RCT of 60 patients treated in the same way. Patients were divided into two subgroups: 131 patients (65 control group) with high degree of exposure (type IIIA and IIIB) and 113 patients (48 control group) with low degree of exposure (type I–II). In the "high degree of exposure" subgroup the percentage of further surgeries and infection was lower for the BMP-2 group (9% vs. 28%, $p = 0.0065$, 21% vs. 40%, $p = 0.0234$, respectively). In the "low degree of exposure" subgroup better results were observed in the BMP-2 group with no significant differences. The authors concluded that these results could be determined by the low grade of exposure and the limited number of patients. BMPs were used in selected cases of open fractures treated with external fixator. In a retrospective study, Ristiniemi et al.[30] evaluated the use of