CURRENT CONCEPTS REVIEW

Available Findings Fail to Provide Strong Evidence of the Role of Bone Morphogenic Protein-2 in Femoral Head Osteonecrosis

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Abstract

Despite widespread research on non-traumatic femoral head osteonecrosis (FHON), there is no consensus about preventative treatment options. Insufficient blood supply and increased intra-osseous pressure are the initiating events in the majority of cases. BMPs are growth factors that belong to the transforming growth factor β (TGFβ) superfamily. Two specific formulations of BMPs have already been approved by the FDA: 1. BMP-2 (Infused, Medtronic) for the treatment of tibial open fractures and spinal fusion; 2. BMP-7 (OP-1, Stryker) in the setting of long bone non-unions. To our knowledge there is no published work reviewing the utility of BMP-2 in the setting of FHON.

Online databases (EMBASE, Cochrane, MEDLINE and PubMed) for literature relating to the use of BMP-2 in the treatment of FHON on 2nd June 2017.

Animal studies: A total of 169 animal subjects with induced FHON were treated with BMP-2 in all the included in vivo studies.

Improved histological parameters, areas of revascularization, areas of new bone formation and osteoid deposition were seen in all studies. The number of osteoclasts decreased post operatively, in the ibandronate and BMP-2 group.

Human studies: In combination, 96 human hips were treated in two studies utilizing BMP-2 and mean follow-up was at least five years. Success rate of BMP-2 was above 80 % (based on Harris score and WOMAC score) in both studies. Both are level III studies.

The present review of animal and clinical studies could not find well-designed prospective comparable studies with large sample size and preliminary evidence is not sufficient to supports the utilization of BMP-2, and its impact on the midterm outcomes of FHON.

Level of evidence: III

Keywords: BMP-2, Femoral head, Osteonecrosis

Introduction

Despite widespread research on non-traumatic femoral head osteonecrosis (FHON), there is no consensus about preventative treatment options. Insufficient blood supply and increased intraosseous pressure are the initiating events in the majority of cases. This creates an ischemic environment within cancellous bone and bone marrow, leading to necrosis and a cascade inflammatory that ultimately results in

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osteoclastic bone resorption. As the disease progressed, subchondral collapse and subsequent secondary arthritis will occur. This has cause significant morbidity given younger patients are typically affected (1, 2). There is abundance of studies in the literature with conflicting recommendation regarding the use of various treatment options including: core decompression (CD), cancellous bone grafting, non-vascularized structural allograft use, and free vascularized grafting (3, 4). Based on recent developments in the field of regenerative medicine, it is anticipated that the future treatment of FHON will be focused at a cellular level (5).

In 1965, Marshal Urist first discovered the presence of osteoinductive substances in the extracellular matrix that have come to be known as bone morphogenetic proteins (BMPs) (6). BMPs are growth factors that belong to the transforming growth factor β (TGFβ) superfamily. Experimental studies have shown that naturally occurring mutations in BMPs genes plays critical roles in musculoskeletal, neural and cardiac development, as well as also infantile bone formation. Two specific formulations of BMPs have already been approved by the FDA: 1. BMP-2 (Infused, Medtronic) for the treatment of tibial open fractures and spinal fusion; 2. BMP-7 (OP-1, Stryker) in the setting of long bone nonunions (7). According to recent reports, BMPs are not only osteoinductive, but also act as a potent stimulator of angiogenesis (8). Given these mechanisms activity, it has the potential to address two major pathophysiological factors contributing to FHON. The published literature has multiple reports that summarize the role of BMP-2 in the context of bony defects, fracture nonunions and spinal fusion surgery (9). However, to our knowledge there is no published systematic review which evaluate the quality of existing evidence about the utility of BMP-2 in the setting of FHON. We have performed a narrative review on the efficacy of BMP-2 as a treatment option in FHON.

Materials and Methods

Search strategy

Two reviewers (A.A, H.V) searched four online databases (EMBASE, Cochrane, MEDLINE and PubMed) for literature relating to the use of BMP-2 in the treatment of FHON on 2nd June 2017.The key words used were 1. osteonecrosis; 2

Bone Morphogenic -2; 3.femoral head. PRISMA guidelines were adhered to when designing this study (10).

The inclusion criteria were: (i) all levels of evidence; (ii) experimental and human studies; (iii) English language publications; (iv) studies of femoral head osteonecrosis receiving BMP-2. Prior systematic and simple review articles were excluded from our search. There was defined no limitation with respect to the year of publication.

Study screening

The two reviewers (A.A, H.V) independently screened titles, abstracts and full texts of the retrieved studies were reviewed. Furthermore, manually searched reference lists of reviewed articles were reviewed to identify additional eligible studies. In addition to duplicate studies, those study with combination therapy other than BMP-2 or studies without a clear outcome measurement were removed. Any article eligibility disagreement that not resolved between two reviewers was resolved by the senior reviewer (A.P).

Quality assessment

Due to the lack of available evidence about our study subject in the published literature, and a predominance of animal *in vivo* studies, we could not assess the quality of all included studies using the Methodological Index for Non-Randomized Studies (MINORS) Criteria (11). Since the MINORS criteria could not be completed for included basic science studies evaluated the level of evidence and quality according to Sackett description method (12).

Data extraction

Three authors (A.P., K.G., and H.V.) extracted data from the final pool of relevant articles. Information was obtained about the author, publication date, sample size, age and gender of patients, methodology and study design, and level of evidence, interventions, and adverse outcomes. For the basic science studies, we collected the animal model used, key findings, and limitations of each study. Beside the technique of treatment and demographic data for each enrolled study, preoperative outcome measurements such as Harris Hip Score (HHS), West Ontario McMaster arthritis Index (WOMAC) were collected if applicable and in animal studies material properties and evidence of any changes in the progress/ improvement of FHON were collected.

Results

The initial literature search yielded 66 studies. 15 were duplicated articles from different sources. After screening titles and abstracts, 41 articles did not meet the inclusion criteria were excluded. Further screening of the full texts of the10 remaining studies, resulted in the exclusion of 4 articles (3 combination therapy other than BMP-2 ,1 outcome not included). One further study was identified by during full text review by examination of cited references. Following the above process, a total of seven were identified that were published between 2004 and 2016. These studies comprised two clinical studies and five *in vivo* experimental animal studies.

Animal studies

A total of 169 animal subjects with induced FHON were treated with BMP-2 in all the included *in vivo* studies, with doses ranging from 0.5µg to 1 mg, and ages between 5 weeks and 8 months (13-16). FHON was surgically induced in all studies according to same technique (13, 14). Two of these studies utilized plain radiographic imaging to evaluate postoperative femoral head shape and other characteristics. One study employed additional CT scan analysis to provide precise structural and quantitative radiological assessment of newly formed bony material at the necrotic site (15, 16). In one study the sphericity of femoral head and head deformity was evaluated

arthroscopically (18). All studies reported improved histological parameters to find areas of revascularization based on the presence of blood vessels in the marrow space and the areas of new bone formation based on bone volume, number and thickness of trabeculae, as well as of osteoid deposition. Furthermore Vandermeer et al also found that the number of osteoclast**s** decreased post operatively, in the control group (ibandronate) and BMP-2 group (16). All of the included animal studies had control groups to enable comparisons and increase the validity of findings.

Human studies

We found only two clinical studies that used BMP-2 in patients with osteonecrosis [Table 1]. The level of evidence in both of these studies was III, the first one was a retrospective stuy on 15 patients (17 hips) with symptomatic osteonecrosis whom treated with a combination of core decompression fibular allograft and 50 mg of human BMP . The second study was performed in a group of patients (most of them was SARS survivors who had received high dose corticosteroid pulse therapy) .In combination, 53 hips were treated with BMP-2 and mean follow-up was at least five years (19, 20). Success rate of BMP-2 was above 80 % (based on Harris score and WOMAC score) in both studies. 18 of 19 patients (95%) in both studies had either stage IIA (Ficat) or Stage IIb (ARCO) showed good and excellent efficacy of BMP-2 treatment, while only 61 % of patients with higher stage of disease preoperatively achieved good and excellent results. Treatment success was closely related to the stage of the disease. Sun *et al*. showed that the roundness and complete repair of femoral head in 94% of hips. Postoperative outcome were assessed using standardized questionnaires (Harris score or WOMAC) that showed statistically significant improvement in all scores, activity level and pain.

Safety and tolerability of BMP-2

Heterotopic ossification (HO) was highlighted in two animal studies as a complication of BMP-2 treatment (14, 15). No intra-operative complications were observed during operation in both human studies. HO was seen postoperatively in two out of 53 (3.8 %) hips treated with BMP-2, however this was also seen in one out of 43 hips (2.3 %) the control group who were treated by impaction

Table 1. Selected articles

Author/year	Area	Level of evidence	Number of hips/ patients	Mean Age	Gender (F/M)	Stage	Etiology	Mean Follow-up (m)	Treatment/ procedure	Findings/ Conclusion
Lieberman/ 2004	USA	III	17/15	47y	60%/40%	Ficat IIA-III	Steroid (main)	53 m	CD + fibular allograft+ 50 mg BMP-2	82.4% had a successful clinical results (HHS >80)
Sun/2014	Asia	III	79/46	31y	57 %/43%	ARCO (IIb-IIIa) and CJFH (C-L3)*	Steroid (main)	73m	Group1:debridement+IBG**+rh BMP-2*** Group2: debridement+ IBG	82% vs. 72% good and excellent results in rhBMP-2 group
Zhou/2014	Asia	Basic science	74/74	6-8 weeks	Male rats	N/A	Surgical induced	8 weeks	-Group1:sham group, 2:BSA # 3: BMP-2-injected 4:a COMP-Ang1##+ BMP-2-injected - Injection to the epiphysis	combined intraosseous injection of COMP-Ang1 and BMP-2 effectively repaired ischemic damage by inducing angiogenesis and osteogenesis
Vandermeer/ 2011	USA	Basic science	22/22	6-8 weeks	Male piglets	N/A	Surgical induced	8 weeks	Group1:normal, 2:treated with saline solution,3: treated with ibandronate, 4: treated with ibandronate + BMP-2	better preservation of the femoral head shape, trabecular bone volume, thickness, and number and for osteoblast surface in the ibandronate +BMP-2 group

Table 1. Continued

Cheng/2014	Australia	Basic science	12/12	6-8 weeks	Male piglets	N/A	Surgical induced	8 weeks	-Group1:Saline ,Group2: rhBMP-2y, 3: rhBMP-2+local Bisphosphonate -Intra-osseous injection	local delivery of rhBMP-2 and bisphosphonates in the sugar-based carrier significantly prevent collapse
Ma/2015	Asia	Basic science	36/36	6 months	Rabbit (GenderN/A)	N/A	liquid nitrogen freezing induced	8 weeks	Group1:CD, 2:CD + BMSCs### ,3:CD+ VEGF ¥ /BMP-2 transfect BMSCs	VEGF/BMP-2 gene transfection strengthened osteogenic effects of BMSCs, and accelerated the bone repair that observed arthroscopically
Aruwajoye/ 2016	USA	Basic science	25/25	5–8 weeks	Male piglets	N/A	Surgical induced	8 weeks	Group1:normal control, 2:untreated, 3:Ibandronate, 4:BMP-2,5: BMP-2 +Ibandronate	BMP-2 and BMP-2 + ibandronate normalize the material properties of bone than ibandronate alone

*China-Japan Friendship Hospital classification system
** Impacted bone graft
***recombinant human BMP-2
Bovine serum albumin
Cartilage oligomeric matrix protein angiopoietin-1
Bone marrow mesenchymal stem cells
¥ Vascular endothelial cell growth factor

bone graft and the difference was not significant (19, 20).

Conversion to hip replacement

Overall 10.4 % of hips went on to undergo total hip arthroplasty at mean 5 year follow-up. More specifically, 9% (7 of 79 hips) in the Sun et al. study and 18 % (3 of 17 hips) in the Lieberman *et al* study were reported.

Discussion

The ultimate goal of hip joint preserving intervention in FHON is to prevent collapse and maintain the congruency, joint space, and femoral head sphericity.

However, long term follow–up of widely accepted traditional treatments like CD and autologous bone grafting shows that these modalities cannot effectively delay the accelerated process of secondary arthritis (21). Recent efforts are focusing on the development of biological strategies to arrest the necrotic process and restore the function of involved areas by enhancing osteogenic activity.

BMPs a potent ability to induce bony regenerations. BMP-2, 4, 7, and -9 have been found to show osteoinductive activity (22- 25). BMP-2 promote the differentiation of mesenchymal cells along the osteoblastic lineage and enhance bone formation (26).

Mont et *al*. added BMP to a bone substitute consisting of demineralized bone matrix, to treat osteonecrotic defects of the femoral head and reported about 90 % success rate after mean 4 year follow-up. In 80% of their patients, radiologic evidence of even slight femoral head collapse (less than 2 mm) was absent (27).

In a sheep model of direct ethanol-induced FHON, BMP-2 was applied and showed good healing potential 3-months post-operatively that confirmed with histopathology specimen (28).

All experimental studies that mentioned in Table 1 had sophisticated follow-up including histological and imaging confirmation of femoral head vascularity that increases the value of findings. After use of BMP-2, improved radiological and histological results were demonstrated in 100% of the studies (14-18). One study reported significant prevention of femoral head collapse (14).

Lieberman was the first investigator who reported the successful implementation of BMP-2 in patients with FHON. He mixed water soluble BMP, purified from human

bones, with bone allograft and implanted the mixture using an impacted bone grafting technique into 17 osteonecrotic hips with FHON. Patients were followed for a mean period of 53 months and finally 86 % of femoral head preserved without significant collapse. Pain was significantly decreased among BMP treated patients and daily activity level was higher post operatively, in comparison the success rate of CD in literature is very inconsistent (from 29% to 83%) (20, 29).

Despite these exciting results, lack of randomized clinical trials about BMP-2 administration in FHON and limited number of clinical studies in human subjects (61 patients) the lack of a control cohort in an included clinical study limits the validity of conclusions that we could draw. Due to these limitations, it would be inappropriate to subject the data to meta-analysis.

Patients suffering from FHON especially in pre-collapse stages need a standard method of treatment to prevent further progression and preserved the hip joint to a higher age of replacement. The present review concludes that although preliminary evidence supports the efficacy of utilization of BMP-2, but there is no strong evidence for its effects. So, high level of evidence prospective large sample studies should be conduct to confirm its efficacy.

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