Review article

The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillofacial trauma

A.S. Herford

Department of Oral and Maxillofacial Surgery, Loma Linda University, Loma Linda, CA, USA

A R T I C L E   I N F O

Article history:
Received 9 May 2016
Received in revised form 26 November 2016
Accepted 29 November 2016
Available online 9 February 2017

Keywords:
Recombinant human bone morphogenetic protein-2
Maxillofacial trauma
Clinical application

A B S T R A C T

In recent years, recombinant human bone morphogenetic protein-2 (rhBMP-2) has been introduced as a therapeutic option in the treatment of several congenital and acquired craniofacial defects. Although there have been promising clinical results, the international literature still lacks complete guidelines, including limits and indications for the use of rhBMP-2. The possible indications for rhBMP-2 in patients undergoing facial trauma are discussed in this article.

© 2017 Production and hosting by Elsevier B.V. on behalf of Daping Hospital and the Research Institute of Surgery of the Third Military Medical University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Facial trauma management

Trauma is among the top five causes of death in the world, showing different incidence rates from one country to another.1,2 Treatment and management of trauma involving craniofacial region still represents a challenge, due to the presence of important anatomical structures. This part of the body includes, in fact, not only vital organs, but also sensorial and motor systems as visual, auditory, olfactory and speech, composed by both numerous organs located in maxillofacial bones. Moreover, maxillofacial region is the most relevant area concerning the psychological and social aspects. Facial physiognomy, in fact, is used for both self and interpersonal identification, and social relationships; any damage to this region may cause an imbalance in mental health context. The different rates of resistance and elasticity, associated to the position within the district and the shape of the bone itself, are related to the highest incidence of fractures in the mandibular and nasal bones.2

There are several causes of maxillofacial fractures, such as motor vehicle accidents, car crashes, sport activities, fights, etc.2 Trauma affects one out of every three children every year. Unintentional injuries are responsible for almost 90% of all pediatric deaths,3 and the head region constitutes the most affected area in pediatric patients.4-6 The analysis of gender and age distribution showed that the highest prevalence of craniofacial trauma involved young male victims. This can be related to sociocultural behavior, like the need to experience risk, beyond the abuse of alcohol or drugs.4-8 Other reasons, like the major physical activity in heavy works or sports, performed often by young men, can explain the strong correlation; though, the reason why trauma represents one of the first death causes in young population may be also correlated to the low rate of slow progressive diseases, like cancer, atherosclerosis or cardiovascular diseases that usually require years to show the first clinical symptoms. For the mentioned reason and the early occurring age, craniofacial trauma can be associated with severe temporary or permanent sequels, including physical, emotional, social, and economic damage as well, represented by medical care expenses for a long-term period.3,8

Tissue engineering reconstructive options

Although several papers have been published regarding maxillofacial trauma, the topic is still debated and discussed frequently in the literature. Among various solutions proposed, recombinant human bone morphogenetic protein-2 (rhBMP-2) represents a new but already well described therapeutic option, which has showed promising results. Autologous blood-derived products that have recently become commercially available do not contain BMP and have not been shown to be capable of inducing newly formed bone in the standard rat subcutaneous implant model of osteoinductivity.
BMPs are members of transforming growth factors-beta (TGF-beta) group and play an important role in embryonic development including brain and bone formation. At present, nearly 20 different BMPs have been identified, but only BMPs-2, -4, -6, and -7 have been shown to have significant osteoinductive properties. rhBMP-2 has been shown to successfully reconstruct defects ranging from isolated areas of the jaw to the entire restoration of defects. An advantage of rhBMP-2 is that it does not require a donor site, with de novo bone formation and no need for a bone graft. It has also been observed how rhBMP-2, respecting native BMP, is more effective in the bone fracture healing, to shorten the consolidation phase. For these reasons, patients can return to normal life earlier, and the hospital stay is reduced. An adjunctive benefit of rhBMP-2 is represented by its ability to help soft tissue healing as well as in maxillofacial region.

Clinical application of rhBMP-2

rhBMP-2 in craniofacial trauma

The effectiveness of rhBMP-2 when utilized for reconstructing mandibular continuity defects has previously been described. Boyne in a randomized controlled trial demonstrated de novo organ tissue growth in humans from a recombinant human protein; authors underlined how rhBMP-2/ACS safely induced adequate bone for the placement and functional loading of endosseous dental implants in patients requiring staged maxillary sinus floor augmentation. In another study published in 2007, the bony regeneration of premaxillary clefts in humans using rhBMP-2 in a collagen sponge carrier was evaluated; authors concluded that clefts of the anterior maxilla can have complete osseous regeneration induced by rhBMP-2 as an effective alternative to conventional anterior iliac particulate marrow cancellous bone grafts. rhBMP-2 also showed great results when applied in reconstruction of large defects occurring to mandible after tumor resection and osteonecrosis treatment.

While BMP could be an effective aid for the treatment of craniofacial trauma in adults, further considerations must be taken when the patient is still in a growing age. FDA established that rhBMP-2 is contraindicated in patients who (1) are pregnant, (2) may be allergic to any of the materials contained in the devices, (3) have an infection near the area of the surgical incision, (4) have had a tumor removed from the area of the implantation site or currently have a tumor in that area, or (5) are skeletally immature. The general use of BMP-2 in immature patients is not recommended, due to the possible insurgence of side effects and the limited experience. Guidelines for age, weight and level dependent dosage of rhBMP-2 in the pediatric patients are not present in literature yet.

Although extensive data on rhBMP-2 use in immature patients are lacking, several studies described the off-label use of rhBMP-2 to achieve spinal fusion in children with compromised bone healing. Moreover, concerning the maxillofacial district, a case of a 14 female who had complete regeneration of a mandibular defect with an off-label use of rhBMP-2 has been reported. Even if Boyne has shown that pediatric patients can be able to achieve a complete osseous regeneration without bone grafting after a large continuity mandibular resections, it is hard to imagine the same degree of bone regeneration without the aid of rhBMP-2. Furthermore, the surgical treatment itself sometimes may interfere with the growth of pediatric patients. Children show faster healing, also due to an osteogenic potential greater than adults. Therefore, fractures in children must be treated earlier.

The treatment method applied is often modified according to the child’s age and development. Bone morphogenic proteins possess good osteoinductive properties that enhance healing and are used in the treatment of adult patients with recalcitrant non-unions and spinal fusion procedures successfully to facilitate union/fusion. Manufacturers of commercially available rhBMP-2 have stated that it is contraindicated for use in the pediatric population because they have not been able to provide data that establish the safety and efficiency of BMP-2 in children below 18 years of age. The possibility of selecting a conservative treatment versus an open surgical approach is quite debated. The application and the development of BMP-2 for maxillofacial trauma can play an important role for the management of large maxillofacial defect due to traumatic event.

The choice to treat craniofacial fractures in a closed approach may cause severe facial deformities, which are extremely difficult to correct in the future. The surgeon should analyze the risks of impacting skeletal growth versus obtaining acceptable stability and reduction for healing. The avoidance of the sequela of nonoperative treatment and its effects should be avoided for the severe fractures if at all possible. Surgeon must evaluate facial growth, development of the paranasal sinuses and the dental status. The surgeon must consider the general situation of the patient, evaluating maintenance of the airway, balance of fluid and electrolyte levels and adequate nutritional intake during treatment. Resorbable plates are applied in cases without major displacement and comminution. There has been some discussion regarding the use of resorbable plates and screws in pediatric facial fractures. Some authors recommend the use of resorbable plates and screws for growing patients whereas others do not.

rhBMP-2 in orthopedic trauma

rhBMP-2 has been used in orthopedic trauma surgery to treat tibia fractures. Covender et al, in a clinical trial, used rhBMP-2 associated with unreamed nails in open tibia fractures for the first time. During bone formation, BMP-2 plays a fundamental role in a complicated cascade of events that involves a number of several stimulatory factors and cells types. Even if BMP-2 exhibits direct action in recruiting cells to the area and stimulating cell differentiation, the natural biology of bone formation remains intact. Those growth factors are therefore thought to initiate, stimulate and increase the normal bone formation cascade. They showed statistically significant reduction of secondary interventions, which was the main parameter taken in consideration in this study. Moreover, secondary clinical outcomes like hardware failures, fracture healing time, infection wound healing were significantly better when the rhBMP-2 was utilized. Aro et al instead observed that the application of a dose of 1.5 mg/ml rhBMP-2, in association to a reamed nail fixation, for the treatment of open tibia fractures does not significantly shorten the healing time. They also found similar infection rates in the control (11%) compared to the rhBMP-2 group (19%). Recently, Alt et al evaluating both clinical and economic aspects, investigated the effectiveness of rhBMP-2 for tibia fracture treatment again. They highlighted how the use of rhBMP-2 reduces secondary interventions in patients with grade III open tibia fractures treated with an unreamed nail. Furthermore, they confirmed the ability of rhBMP-2 to shorten healing time (even if the difference observed was not significant) and sequentially, to impact the economic aspect, like reduction of health costs and productivity loss. Even if application of rhBMP-2 sometimes showed unclear outcomes, undoubtedly, it has still the potential to bring some advantages in complex clinical situation and trauma.

Experiences in the Loma Linda Oral and Maxillofacial Surgery Department and future perspectives

Currently the existing problems related to rhBMP-2 application in oral maxillofacial surgery and trauma are well documented.
Several tests were performed to determine the effects of rhBMP-2 on fertility reproduction and perinatal toxicity. All those researches demonstrated how the treatment of gravid rabbits with those growth factors did not result in maternal toxicity or gross fetal abnormalities. Moreover, toxicology studies using intravenous administration of rhBMP-2 have demonstrated no toxic effects at doses much higher than those recorded in the clinical application for the bone trauma management. Some journal articles have reported the presence of BMP-2 in a number of human neoplasms. However, those growth factors have not been suggested to play a role in the primary neoplastic process.

rhBMP-2 showed the potential to be an effective therapeutic option for treatment of many trauma and craniofacial bone defects. Future studies, investigating the long-term effects of rhBMP-2 in large samples, may help to provide scientific evidence in trauma treatment. However, more clinical multi central trials need to be realized in order to be effective those potential therapeutic device.

The Loma Linda Oral and Maxillofacial Surgery Department is today a referring center for the use of growth factor in oral and maxillofacial surgery. Firstly Dr. Boyne, Loma Linda University Professor emeritus, on 1996 published a pilot study performed on adult male Macaca fascicularis (rhesus) monkeys in order to observe the effect of two dose ranges of rhBMP-2 on bone regeneration following bilateral hemimandibulectomy. The result of this work indicates that rhBMP-2 can bring about osseous regeneration of critical sized hemimandibulotomy defects in rhesus monkeys.

Ten years later, after several animal research and after the FDA release, BMP-2 has been currently used in the management of cranio-maxillofacial critical size defect. From 2007 those growth factors have been used for the management of the cleft palate in young patients. Clefts of the anterior maxilla can have complete osseous regeneration induced by rhBMP-2 as an effective alternative to conventional anterior iliac partite marrow cancellous bone grafts. In my opinion, and accordingly with Urist, BMP-2 gives the surgeon the possibility of having the control of osteogenesis. However even if the cost is still high, the application of the growth factors represents the future for avoiding large bone grafting procedure reducing the discomfort of the patient. Future studies about the ideal carrier should be performed in order to better manage the action and the release of those powerful proteins.

References

1. Heron M. Deaths: leading causes for 2012. Natl Vital Stat Rep. 2015;64:1—93.
2. Rowe NI, Williams. Maxillofacial injuries the di. 1986:21—232.
3. Atabaki SM. Pediatric head injury. Pediatr Rev. 2007;28:215—224.
4. Alhabban S, Zamakhshary M, Alnaimi M, et al. Epidemiology of traumatic head injury in children and adolescents in a major trauma center in Saudi Arabia: implications for injury prevention. Ann Saudi Med. 2013;33:52—56. http://dx.doi.org/10.1144/0256-4947.2013.52.
5. Calvert S, Miller HE, Curran A, et al. The King’s Outcome Scale for Childhood Head Injury and injury severity and outcome measures in children with traumatic brain injury. Dev Med Child Neurol. 2008;50:426—431. http://dx.doi.org/10.1111/j.1469-8749.2008.02061.
6. Cavalcanti AL, Barros de Alencar CR. Injuries to the head and face in 0—4-year—old child victims of fatal external causes in campina grande, PB, Brazil. Turk J Pediatr. 2010;52:612—617.
7. Acton CH, Nixon JW, Clark RC. Bicycle riding and oral/maxillofacial trauma in young children. Med J Aust. 1996;165:249—251.
8. Anderson PJ. Fractures of the facial skeleton in children. Injury. 1995;26:47—50.
9. Lavery K, Swain P, Fabb D, et al. BMP-2/4 and BMP-6/7 differentially utilize cell surface receptors to induce osteoblastic differentiation of human bone marrow-derived mesenchymal stem cells. J Biol Chem. 2008;283:20948—20958. http://dx.doi.org/10.1074/jbc.M800850200.
10. Cicciò M, Herford AS, Cicciò D, et al. Recombinant human bone morphogenetic protein-2 promote and stabilize hard and soft tissue healing for large mandibular new bone reconstruction defects. J Craniofac Surg. 2014;25:860—862.
11. Boyne PJ. Application of bone morphogenetic proteins in the treatment of clinical oral and maxillofacial osseous defects. J Bone Jt Surg Am. 2001;83:5146—5150.
12. Boyne PJ, Lilly LC, Marx RE, et al. De novo bone induction by recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary sinus floor augmentation. J Oral Maxillofac Surg. 2005;63:1693—1707.
13. Herford AS, Boyne PJ, Rawson R, et al. Bone morphogenetic protein—induced repair of the maxillary cleft. J Oral Maxillofac Surg. 2007;65:2136—2141.
14. Herford AS, Cicciò M, Recombinant human bone morphogenetic protein type 2 jaw reconstruction in patients affected by giant cell tumor. J Craniofac Surg. 2010;21:1970—1975. http://dx.doi.org/10.1097/SCS.0b013e3181f02fa.
15. Cicciò M, Herford AS, Jaudzibals G, et al. Recombinant human bone morphogenetic protein type 2 application for a possible treatment of bisphosphonates—related osteonecrosis of the jaw. J Craniofac Surg. 2012 May;23(3):784—788. http://dx.doi.org/10.1097/SCS.0b013e318244ddd4.
16. Lu DC, Sun PP. Bone morphogenetic protein for salvage fusion in an infant with Down syndrome and craniovertebral instability. Case report. J Neurosurg. 2007;106:480—483.
17. Olugbami CO, Solanki GA. Use of recombinant human bone morphogenetic protein—2 to enhance posterior cervical spine fusion at 2 years of age: technical note. Pediatr Neurosurg. 2008;44:393—396. http://dx.doi.org/10.1159/000104909.
18. Milanov KV, Philipp Junkel P, Sneedek R. The use of recombinant human BMP as a salvage procedure in the pediatric spine: a report on 3 cases. Eur Spine J. 2010;19:5135—5139. http://dx.doi.org/10.1007/s00586-009-1179-2.
19. Boyne PJ. The restoration of resected mandibles in children without the use of bone grafts. Head Neck Surg. 1983;6:626—631.
20. Herford AS, Tandon R, Pivetti L, et al. Treatment of severe frontonasal fractures in growing patients: a case series evaluation. Chin J Traumatol. 2013;16:199—203.
21. Wheeler J, Phillips J. Pediatric facial fractures and potential long-term growth disturbances. CMAJ. 1996;154:513—522. http://dx.doi.org/10.1503/cmaj.19960412.
22. Eppley BL. Use of resorbable plates and screws in pediatric facial fractures. J Oral Maxillofac Surg. 2005;63:385—391.
23. Cavender S, Cimma C, Genant HK, et al. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Jt Surg Am. 2002;84:2123—2132.
24. Aró HT, Cavender S, Patel AD, et al. Recombinant human bone morphogenetic protein-2: a randomized trial in open tibial fractures treated with reamed nail fixation. J Bone Jt Surg Am. 2011;93:801—808. http://dx.doi.org/10.1002%28j%29.1.17535.
25. Alt V, Borbman B, Eicher A, et al. Effects of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) in grade III open tibia fractures treated with unreamed nails-A clinical and health-economic analysis. Injury. 2015;46:2267—2272. http://dx.doi.org/10.1016/j.injury.2015.07.015.
26. Lee DY, Cho TJ, Lee HR, et al. Disturbed osteoblast differentiation of fibroblast hamartoma cell from congenital pseudarthrosis of the tibia associated with neurofibromatosis type I. Clin Orthop Surg. 2011;3:230—237. http://dx.doi.org/10.4055/clos.2011.3.3.230.
27. Byrom HM, Lee MHL, Kim YJ. Critical molecular switches involved in BMP-2—induced osteogenic differentiation of mesenchymal cells. Gene. 2006;366:51—57.
28. Lee EH, Lim HC, Hong JY, et al. Bone regenerative efficacy of biphasic calcium phosphate collagen composite as a carrier of rhBMP-2. Clin Implantol Res. 2016;27:e91—e99. http://dx.doi.org/10.1111/clr.12568.
29. Herford AS, Tandon R, Stevens TW, et al. Immediate distraction osteogenesis: the sandwich technique in combination with rhBMP-2 for anterior maxillary and mandibular defects. J Craniofac Surg. 2013;24:1383—1387. http://dx.doi.org/10.1097/SCS.0b013e318292c2ce.
30. Lu Y, Lee JS, Nemke B, et al. Coating with a modular bone morphogenetic peptide promotes healing of a bone-implant gap in an ovine model. PLoS One. 2012;7:e50378. http://dx.doi.org/10.1371/journal.pone.0050378.
31. Boyne PJ. Animal studies of application of rhBMP-2 in maxillofacial recon- struction. Bone. 1996;19:835—925.
32. Niederwanger M, Urist MR. Demineralized bone matrix supplied by bone banks for a carrier of recombinant human bone morphogenetic protein (rhBMP-2): a substitute for autogenic bone grafts. J Oral Implantol. 1996;22:210—215.