The Role of rhBMP-2 in Oral and Maxillofacial Reconstruction

4

Alan Herford and Isaac Lowe

4.1 Introduction

For many maxillofacial reconstructions, the preferred method for reconstruction has incorporated autografts harvested from various parts of the body. This includes microvascular free flap as well as other types of tissue transfers. Recently, this standard has been challenged by the rapid increased research into osteogenic factors in an attempt to eliminate the need for a donor site and associated morbidities such as longer operating time, secondary surgical site, higher amounts of blood loss, donor site pain, ambulation, infection, impaired wound healing, hematoma, and donor site fracture [1–3]. Donor site pain is the most common postoperative complication in regard to ICBG harvest, and current research suggests a long-term complication rate ranging from 25 to 46.5% [4–6]. This means, for ICBG cases alone, we can expect an average of one patient in four experiencing a complication which may possibly last long term [4–6]. Currently research is focusing on numerous osteogenic factors (BMP-2, PRP, PDGF, TFG-β, and IGF) with recombinant human bone morphogenetic protein-2 (rhBMP-2) showing the most promise with regard to bone formation [7].

A. Herford (✉) · I. Lowe
Department of Oral and Maxillofacial Surgery, Loma Linda University, Loma Linda, CA, USA
e-mail: aherford@llu.edu

4.2 What Are They?

BMPs are a family of cytokines, in the TGF-β family, that are involved in angiogenesis, cell apoptosis, inflammation, and the development and maintenance of many processes throughout of the body [8]. BMP's main role, for the limits of the discussion of maxillofacial reconstruction, is the mediation of bone and cartilage formation and maintenance [8, 9]. BMP-2 in particular emerged as a major cytokine of interest, in regard to its potential for clinical application, due to its specific osteogenic properties [3, 8, 9]. Bone grafting in the maxillofacial region is primarily completed via autografting from the iliac crest because the use of other grafting materials (xenografts and allografts) is not considered osteogenic and the body takes longer to replace the grafting material because osteogenic and osteolytic cells need to be recruited to the grafting site and differentiate into mature osteogenic cells before bone turnover can begin. In some cases, a decalcifying stage may be needed before the material can be turned over if the grafting material is calcified adding to the turnover time.

For larger defects such as segmental defects of the jaw, non-autogenous grafts have not been shown to have a high success rate, and thus autografts are indicated. The combination of allografts or xenografts with BMP-2 has shown promise for reconstrution by the addition of a growth factor

© Springer Nature Switzerland AG 2019

J. C. Melville et al. (eds.), *Regenerative Strategies for Maxillary and Mandibular Reconstruction*,
https://doi.org/10.1007/978-3-319-93668-0_4

to non-autogenous grafts, granting osteoconductive properties closer to autogenous grafts.

4.3 How Do They Work?

BMP-2 is uniquely osteogenic, when compared to other growth factors because BMP-2 induces undifferentiated mesenchymal cells to differentiate into osteoblasts and exhibits chemotactic effects toward human osteoblasts and osteoblast progenitor cells in the human marrow [4, 8]. BMP-2 binds to the surface proteins of undifferentiated mesenchymal cells and activates transcription factors SMAD-1, SMAD-5, and SMAD-8 which complexes with SMAD-4 in the cytosol [3, 8, 9]. The complex then travels to the cell's nucleus and activates transcription factors, Runx-2 and TCF/TLEF, to trigger osteoblastic differentiation, maturation, and osteogenic effects (increased production of extracellular matrix, alkaline phosphate, and collagen-1) [3, 8, 9] (Fig. 4.1). BMP-2 also indirectly induces osteoclastic effects through the RANK/RANKL and TRAP mechanisms which facilitates the replacement of grafting material eventually resulting in new bone formation [4, 3, 8, 9]. Because autografts feature no risk of graft rejection and the graft itself intrinsically has osteogenic properties, it's easy to understand why autografting has remained the gold standard for so long. The fact that BMP-2 is osteoinductive is critical because using it with allografting and xenografting materials (which are not inherently

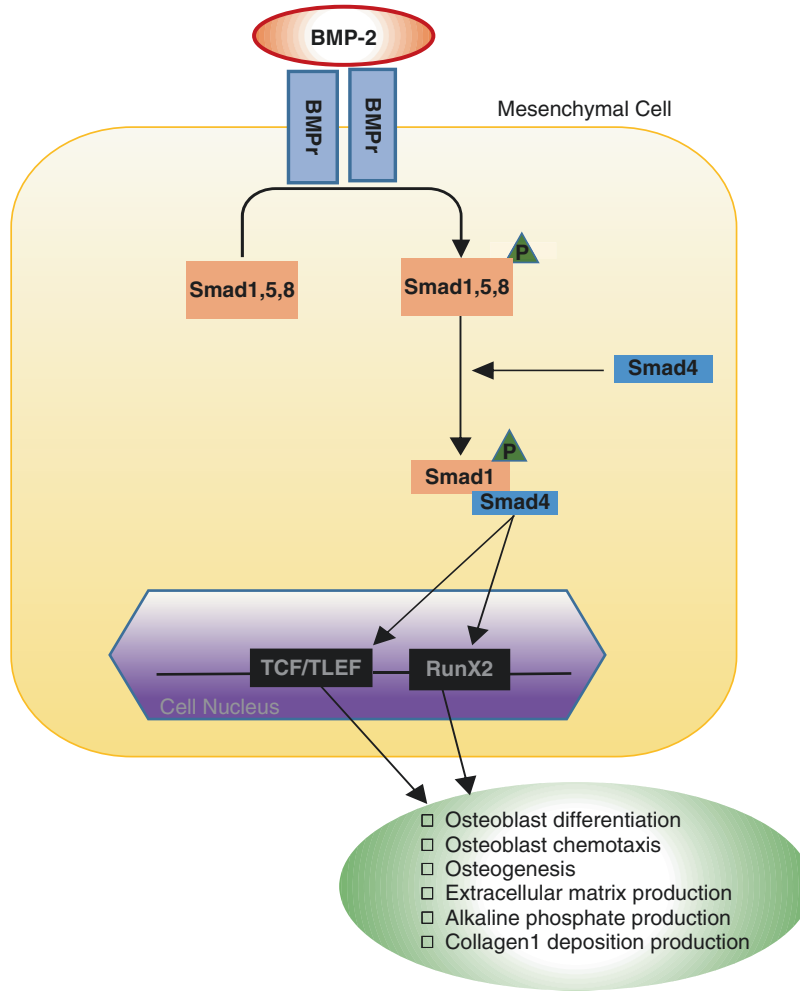

Fig. 4.1 Cartoon describing BMP-2's osteogenic pathway

osteoinductive) potentially accelerates the substitution of the material with natural "self" bone shortening the gap between these materials and autografting [4].

4.4 Clinically What Does It Look Like and How Do I Use It?

For maxillofacial reconstruction cases, rhBMP-2 kits commonly present as a vial of rhBMP-2 and a vial of sterile saline and several ACSs that are easily manipulated to fit into a variety of shapes and sizes. The vials of rhBMP-2 come in concentrations of 1.5 mg/cc which has been found to be the optimum concentration for osteoinductive properties while minimizing postoperative complications in the maxillofacial region [3, 10]. The size and location of the osseous defect and restoration plan typically dictate the amount of rhBMP-2 used for the procedure. The ACS is soaked in the indicated amount of rhBMP-2 for 15 min and placed into the grafting site within 2 hours of opening the kit. The collagen sponge is then cut into small pieces and combined with a "graft extender." This may be either autograft, non-autograft, or both. It is important to mix the sponge throughout the graft materials in order to incorporate the slow release properties of the BMP/ACS graft. When ready, the rhBMP-2/ACS graft material is placed into the defect. In most cases, a titanium mesh and membrane are used to maintain the graft material in the defect and to prevent soft tissue invasion into the grafting site that would normally result in grafting failure or not obtaining an adequate bone volume [4]. Fixation techniques vary in the literature depending on the grafting site [2, 3, 7, 8, 11, 12].

4.5 Does It Work? What Can I Use It For?

Traditionally, research has shown that autogenous grafts are associated with features the greatest success rates, in general for maxillofacial reconstruction, when compared to allografting and xenografting procedures [13, 14]. Research reflects this trend for dental and prosthetic implants in that implants placed in allografted and xenografted bone are slightly less successful than in autografted sites, but depending on the situation, autografting may not always be possible [13, 14]. Autogenous grafting requires more surgical time, more blood loss, and the aforementioned complications [6, 10]. Also, in some situations, there may not be enough available tissue, in terms of volume and quality, to harvest if the defect is too extensive [1–6]. Therefore, even though autografting techniques are slightly more successful, allografting and xenografting can lead to safe and successful outcomes for maxillofacial reconstruction.

Extensive animal studies [4, 7, 8, 10, 11, 15–17] show that rhBMP-2 (INFUSE®) is a successful, safe, and reliable material to use for critical-sized maxillary and mandibular bone defects, maxillary cleft reconstruction [13], and long-term dental implant support and retention [17]. Some animal studies even reported superior results with rhBMP-2 when compared with ICBG for certain procedures [16].

The first human trial using BMPs was conducted in 2001 by Moghaden et al. and showed that BMPs can safely and successfully be used for xenografting in the mandible after healing in the trapezius muscle [18]. A few years later, rhBMP-2 with ACS was also shown to be safe and successful in repairing continuity defects in the mandible [3]. Thus far, the FDA approved rhBMP-2 with ACS use for maxillofacial sinus augmentation in 2007 (INFUSE®) but has been effective in meeting the needs for a variety of osseous maxillofacial reconstruction situations, as an off-label use [2, 3, 7, 8, 11, 12, 19].

More recent research shows rhBMP-2 with ACS and other allografting or xenografting materials features comparable and sometimes superior results compared to the standard ICBG modalities for alveolar cleft repair [2] (Fig. 4.2), localized alveolar bone defects [10] (Fig. 4.3), critical maxillary and mandibular bone defects [3, 4, 12], autogenous sinus augmentations [10], dental endosseous implant placement with restoration [20], xenografting [18], alveolar socket

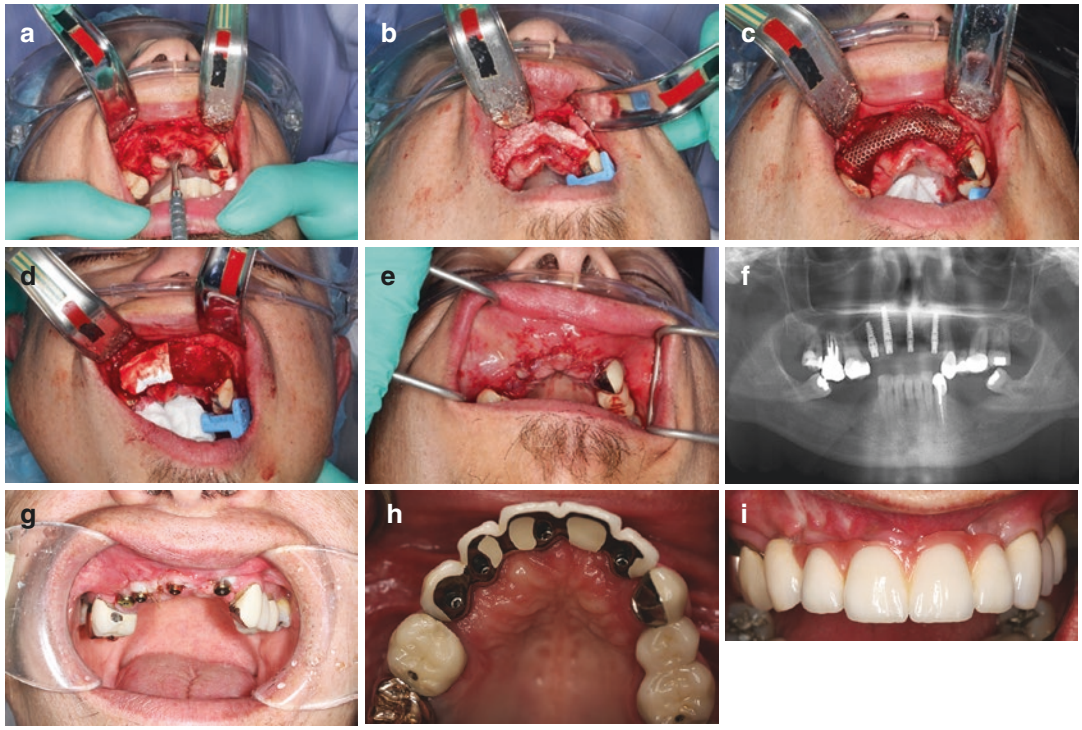

Fig. 4.2 (**a**) Critical maxillary anterior osseous defect spanning tooth #3–11. (**b**) With anterior and posterior flaps reflected, the collagen sponge with rhBMP-2 was placed on the maxillary alveolar ridge. (**c**) Prefabricated titanium mesh placed to retain the graft. (**d**) Resorbable membrane placed over the titanium mesh to prevent soft tissue invasion. (**e**) Primary closure via 3.0 chromic suture. (**f**) One-year follow-up panoramic radiograph after implant placement and osseointegration

preservation [10], and craniofacial defects in general [7, 21]. When rhBMP-2 with ACS is used for alveolar socket preservation (Fig. 4.4), results showed double the amount of bone regeneration compared to empty control sites [10].

Alveolar cleft defect closure with rhBMP-2 and ACS featured no statistically significant difference in success rates, failure rates, and needs for secondary surgery to facilitate hard tissue closure when compared to standard ICBG therapy [2]. For all other aforementioned procedures, case reports and reviews indicate similar success rates, failure rates, and needs for secondary operations when compared to the standard ICBG therapy [2, 3, 7, 8, 11, 12, 19]. Furthermore, there is no evidence to show that rhBMP-2 and ACS use in bone grafting for maxillofacial reconstruction prevents tooth eruption or orthodontic tooth movement [2]. On average, patients were evaluated on a 6- and 18-month basis after surgery was completed and/or after functional loading at the grafting site [2, 3, 7, 8, 11, 12, 19].

Overall, articles report that rhBMP-2 with allo-/xenografting material features excellent grafting volume retention [2, 3, 7, 8, 11, 12, 19, 21]. Histologic evaluation most commonly reports the rhBMP-2 sites being indistinguishable from the "normal bone" [2, 3, 7, 8, 11, 12, 19, 21]. Integration results at grafting sites feature the same if not better results when compared to autografting sites radiographically and histologically [2, 3, 7, 8, 11, 12, 19, 21]. Measurement modalities included histologic sampling (for trabecular pattern, trabecular thickness, and hard tissue volume) and radiologic evaluation (dental radiographs, CBCT scans, panoramics) [2, 3, 7, 8, 11, 12, 19, 21].

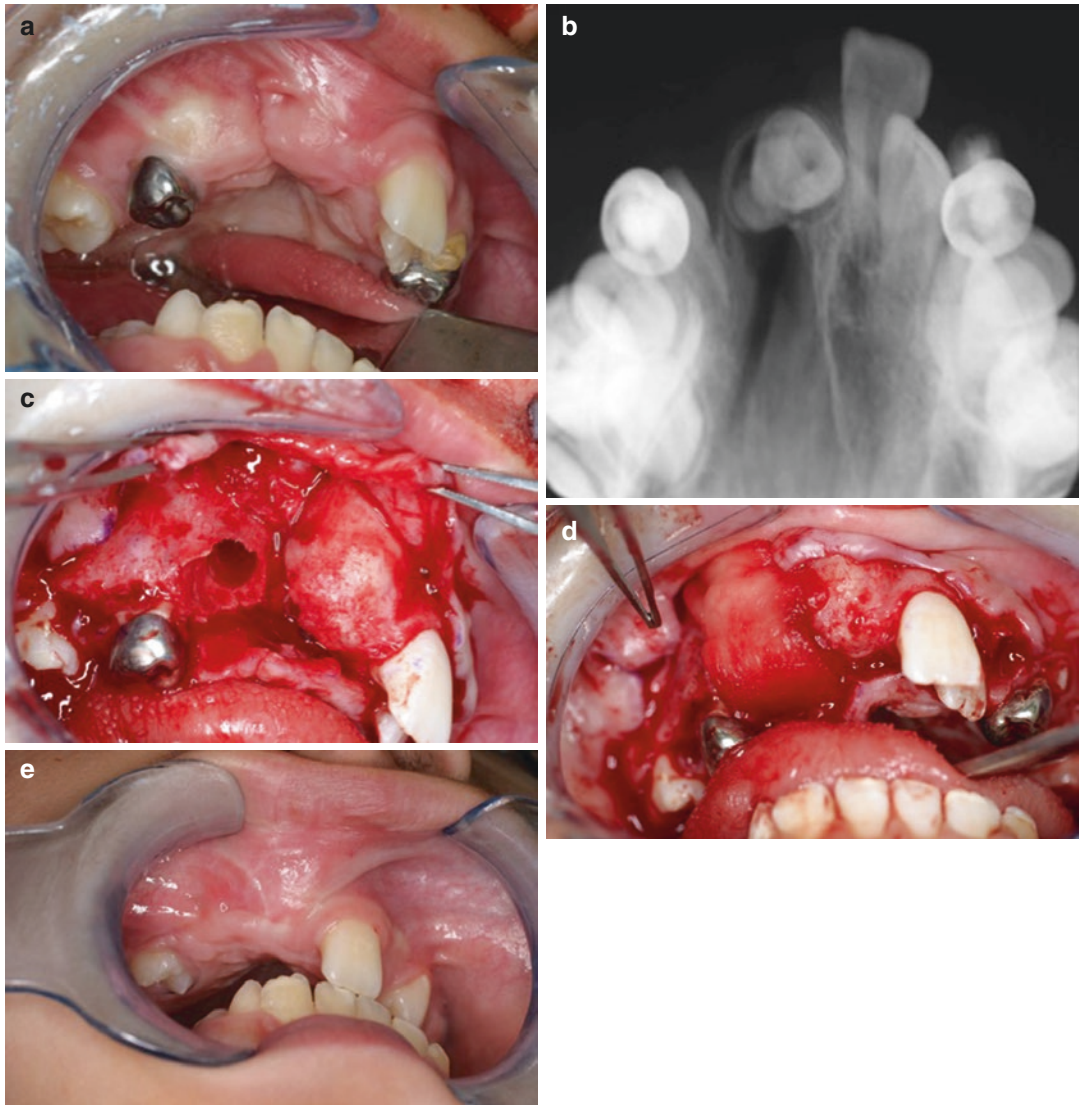

Fig. 4.3 (**a**) Panoramic radiograph showing alveolar cleft defect between teeth #6 and #7. (**b**) Occlusal radiograph showing alveolar cleft defect between teeth #6 and #7. (**c**) Occlusal radiograph after cleft restoration with rhBMP-2/ACS and orthodontic positioning. (**d**) Clinical view of cleft repair after rhBMP-2/ACS and orthodontic correction

4.6 Combination with Autografts

In some cases, it may be preferable to combine autogenous grafts with a growth factor. One example would be those cases which require reconstruction of the mandibular condyle as part of the primary reconstruction [22]. A costochondral graft can be used to reconstruct the joint and limit the risk of ankylosis. An alteration would be to use a prosthesis to replace the joint. Another benefit of adding BMP to an autograft is that it reduces the size of graft harvest [22].

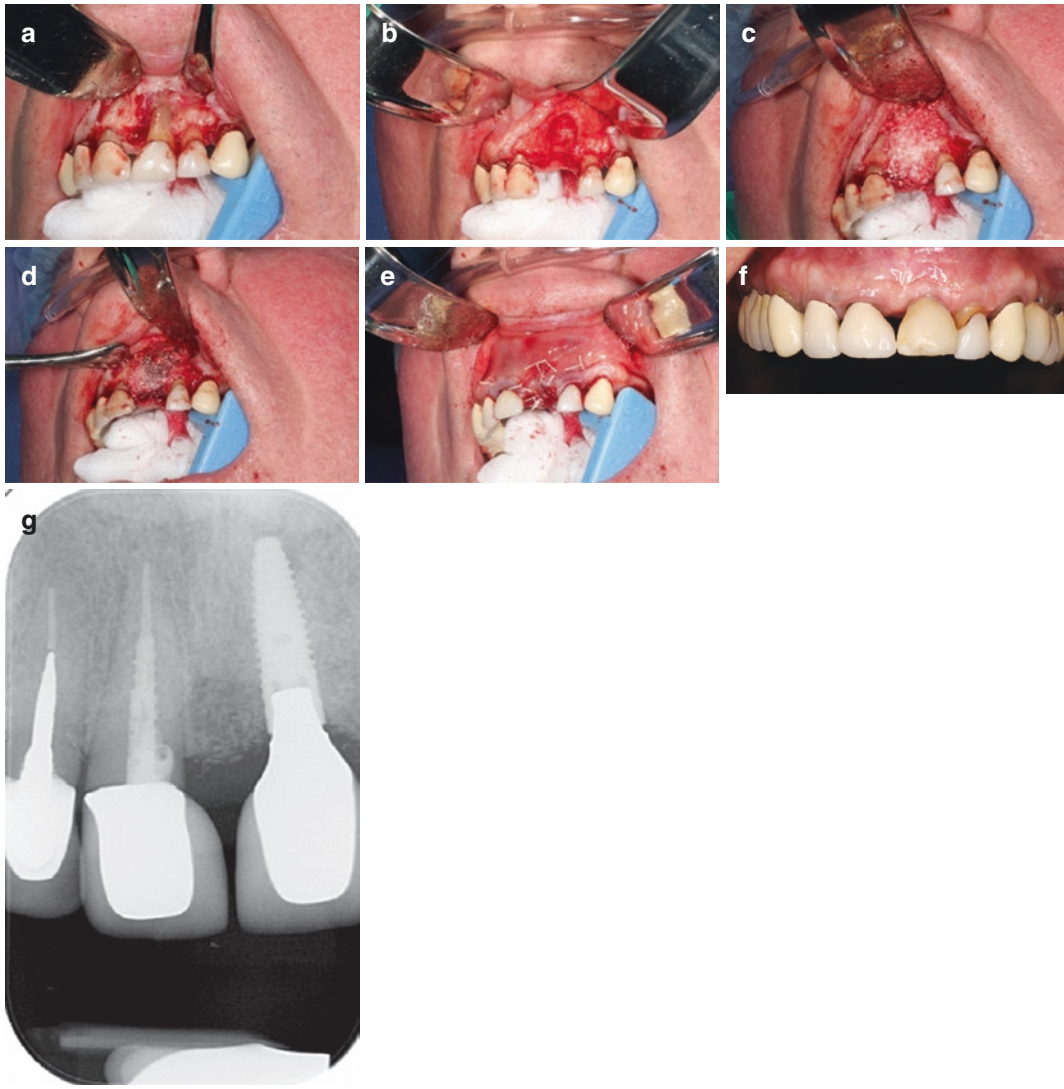

Fig. 4.4 (**a**) Maxillary buccal flap reflected to appreciate the three-walled osseous defect at tooth #9. (**b**) Surgical site after atraumatic extraction of tooth. (**c**) Bone graft with rhBMP-2 placed in the alveolus. (**d**) Adapted titanium mesh fixated. (**e**) Primary closure with 3.0 chromic gut

4.7 Limits, Adverse Effects, and Contraindications with rhBMP-2/ACS

Despite the debate regarding rhBMP-2's success and adverse events rates in animal and human trials, the vast majority of articles show that most of the more serious postoperative complications are primarily seen with spinal fusion cases and not maxillofacial reconstruction [15, 23]. These most common complications for spinal fusion cases with rhBMP-2 are retrograde ejaculation, dysphagia, heterotopic bone formation, hematoma, seroma, osteolysis, and wound complications that all occur in differing rates [15, 23]. For maxillofacial cases, certain postoperative complications, like postoperative infection and wound dehiscence, did not occur at a significantly different rate compared to autografting complication rates [2]. Other adverse events specifically correlated with the use of rhBMP-2 in maxillofacial reconstruction are edema, erythema, and dyspha-

gia which are consistent with BMP-2's inherent role in the inflammatory process [2, 5, 12, 20, 24]. The complication rate for dysphagia ranges from 3 to 85%, with 25% being the most commonly reported. These complications most often are self-resolving, but about 10% require steroid therapy but no other interventions [2, 5, 24]. The rates for significant erythema and edema are much more difficult to quantify.

While the majority of edema and erythema complications self-resolve without the need for intervention and proceed onto successful reconstruction, these complications should be taken seriously because they can be profound [4, 25–27]. Reviews and case reports indicate that the maximum amount of postoperative edema and erythema occurs 3 to 4 days post-op with rhBMP-2 and usually lasts up to 8 days which is not outside the normal range for maxillofacial reconstructions in general anyway [25]. It is difficult to definitively identify the rate of significant rhBMP-2-related postoperative edema and erythema because these are regularly occurring complications when preforming surgery in general. The vast majority of these cases do self-resolve with only a hand full of cases requiring postoperative steroids and did not require any further intervention [2, 3, 5, 7, 8, 11, 12, 19, 21].

The vast majority of serious complications requiring immediate intervention are not related to rhBMP-2. One reported case featured a patient requiring immediate return to the operating room due to postoperative hematoma formation [5]. This complication was attributed to the patient's von Willebrand factor disease and found no relation to the rhBMP-2 used [5]. There was also one case of prolonged intubation attributed to patient's history of obstructive sleep apnea also not related to rhBMP-2 use [2]. That being said, life-threatening situations do occur when using rhBMP-2 that are related to the profound edema discussed earlier. Care should be taken to manage the airway for mandibular reconstruction when utilizing rhBMP-2.

Finally, one article reported a risk but no cases of seroma development as a possible adverse event associated with localized elevated levels of rhBMP-2 [28]. Akeel et al. showed that 10–50 ng/mL rhBMP-2 triggers cell cultures to elevate levels of angiogenic and inflammatory factors (IL-6 and VEGF) via a ROS-dependent mechanism [5]. While the article stated this mechanism might contribute to a risk of seroma formation, it also stated that triggering these angiogenic effects may help potentiate beneficial effects [29].

The contraindications for using INFUSE® are if the operation site is proximal to tumors recently treated and for patients that have a history of allergic reaction, currently pregnant, that have an active infection in the operating site, currently being treated for malignancies [31]. Despite there being a narrow FDA approval for surgical procedures, INFUSE is successfully used in a number of procedures in the head and neck area for a variety of surgical procedures.

There have been FDA warnings that highlight the increased safety risks children face when they undergo spinal surgery with INFUSE® [30]. These warnings are focused on spinal surgeries because there is less space between the spinal cord and the bones surrounding. This warning and increased risk do not extend to its use in pediatric facial surgery patients. However, due to the nature of pediatric surgical cases, complications can turn develop more rapidly compared to adults patients. Subsequently, the safety of BMP in this patient population requires further study [30–33]. BMP is shown to be successful in a variety of procedures for this age group: craniocervical reconstruction, tibial pseudarthrosis, tibial nonunion repair, femoral nonunion repair, and even talonavicular joint repair [32].

Complications for this patient age range resemble those seen for adult patients, primarily associated with profound inflammatory response associated to the use of BMP [32, 33]. The reported overall complication rate with BMP ranges from 20 to 39% with only 8% requiring intervention [32, 33]. The rare cases of intervention for complications are most commonly due to postoperative infection, compartment syndrome, and hematoma with all documented patients recovering successfully after [32, 33]. Retreatment with BMP or repeated exposure is not currently associated with an elevated risk of complications in this age group and is not associ-

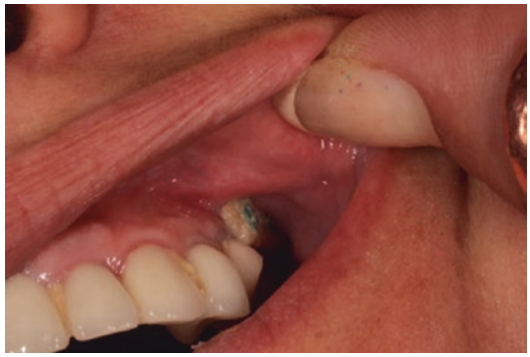

Fig. 4.5 S/p maxillary posterior bilateral rhBMP-2 bone grafting, maxillary left posterior wound dehiscence on 2-week follow-up due to history of smoking and inability to stop during healing period despite informed and understood risks by the patient. Retracted left lip and vestibule to better visualize complication site

ated with the development of cancer [32, 33]. There have been documented cases of patients with neurofibromatosis featuring enlargement of pre-existing intracranial gliomas, but no direct association with the use of BMP has been established [32, 33]. While rhBMP with ACS is a safe alternative to autografting in pediatric patients, caution and the patient's airway should be secured for facial surgery due to the inherent nature of pediatric complications turning severe rapidly.

Overall success and failure rates of bone grafting with rhBMP-2 do not differ at a statistically significant rate from ICBG in the presence of patient risk factors (smoking, alcohol use, hypothyroidism, osteoporosis, diabetes, radiation, and bisphosphonate therapy), but should a patient feature any of these risk factors, they must be informed of the risk of graft failure, postoperative infection, wound dehiscence (Fig. 4.5), delayed healing, and even the need for subsequent grafting [1, 4, 15].

4.8 Conclusion

A variety of maxillofacial defects have been shown to be amenable to reconstruction with BMP-2. RhBMP-2 with allografting or xenografting material offers the benefits of having osseous defects successfully and safely replaced in the human body by the patient's own tissues.

Even though autografting procedures are the current standard for maxillofacial reconstruction that requires bone grafting, we need to continually strive to develop new methods and techniques to reduce the morbidity and burden for our patients. Out of all the current osteogenic mediators being researched, rhBMP-2 with ACS features the most promise and clinically offers comparable results compared to the standard ICBG procedures for a variety of maxillofacial reconstruction cases. While rhBMP-2 with ACS holds great promise as an alternative to ICBG, we need more research into the long-term viability of bone grafting sites accomplished with rhBMP-2 with a variety of alloplastic materials, post-op complication rates, and success rates with greater patient pools in a greater variety of maxillofacial reconstruction defects. For now, rhBMP-2 appears to be an excellent alternative to ICBG, but with more research and time, we may even be able to replace many of the gold standard bone grafting treatment options for maxillofacial reconstruction and eliminate the need for a donor site all together.

References

1. Buser Z, Brodke DS, Youssef JA, Meisel H-J, Myhre SL, Hashimoto R, Park J-B, Tim Yoon S, Wang JC. Synthetic bone graft versus autograft or allograft for spinal fusion: a systematic review. J Neurosurg Spine. 2016;25(4):509.
2. Hammoudeh JA, Fahradyan A, Gould DD, Liang F, Imahiyerobo T, Urbinelli L, Nguyen JT, Magee W 3rd, Yen S, Urata MM. A comparative analysis of rhBMP-2/DBM vs. ICBG for secondary alveolar bone grafts in patients with cleft lip and palate: review of 501 cases. Plast Reconstr Surg. 2017;140:318e.
3. Herford AS, Boyne PJ. Reconstruction of mandibular continuity defects with bone morphogenetic protein-2 (rhBMP-2). J Oral Maxillofac Surg. 2008;66:616.
4. Herford AS, Dean J. Recombinant human bone morphogenic protein-2 (rhBMP-2) used in maxillofacial surgery. J Oral Maxillofac Surg. 2008;16:1.
5. Riederman BD, Butler BA, Lawton CD, Rosenthal BD, Balderama ES, Bernstein AJ. Recombinant human bone morphogenetic protein-2 versus iliac crest bone graft in anterior cervical discectomy and fusion: dysphagia and dysphonia rates in the early

postoperative period with review of the literature. J Clin Neurosci. 2017;44:180.
6. Zhang H, Wang F, Ding L, Zhang Z, Sun D, Feng X, An J, Zhu Y. A meta analysis of lumbar spinal fusion surgery using bone morphogenetic proteins and autologous iliac crest bone graft. PLoS One. 2014;9:e97049.
7. Schilephake H. Bone growth factors in maxillofacial skeletal reconstruction. Int J Oral Maxillofac Surg. 2002;31:469.
8. Reddi AH. Bone morphogenetic proteins and skeletal development: the kidney-bone connection. Pediatr Nephrol. 2000;14:598.
9. Termaat MF, Den Boer FC, Bakker FC, Patka P, Haarman HJTM. Bone morphogenetic proteins. J Bone Joint Surg Am. 2005;87:1367.
10. McKay WF, Peckham SM, Badura JM. A comprehensive clinical review of recombinant human bone morphogenetic protein-2 (INFUSE® Bone Graft). Int Orthop. 2007;31:729.
11. Boyne PJ. Application of bone morphogenetic proteins in the treatment of clinical oral and maxillofacial osseous defects. J Bone Joint Surg Am. 2001;83-A(Suppl 1):S146.
12. Cicciù M, Herford AS, Stoffella E, Cervino G, Cicciù D. Protein-signaled guided bone regeneration using titanium mesh and Rh-BMP2 in oral surgery: a case report involving left mandibular reconstruction after tumor resection. Open Dent J. 2012;6:51.
13. Boyne PJ, Nath R, Nakamura A. Human recombinant BMP-2 in osseous reconstruction of simulated cleft palate defects. Br J Oral Maxillofac Surg. 1998;36:84.
14. Motamedian SR, Khojaste M, Khojasteh A. Success rate of implants placed in autogenous bone blocks versus allogenic bone blocks: a systematic literature review. Ann Maxillofac Surg. 2016;6(1):78–90. https://doi.org/10.4103/2231-0746.186143.
15. Hustedt JW, Blizzard DJ. The controversy surrounding bone morphogenetic proteins in the spine: a review of current research. Yale J Biol Med. 2014;87:549.
16. Toriumi DM, Kotler HS, Luxenberg DP, Holtrop ME, Wang EA. Mandibular reconstruction with a recombinant bone-inducing factor. Functional, histologic, and biomechanical evaluation. Arch Otolaryngol Head Neck Surg. 1991;117:1101.
17. Wikesjo UM, Sorensen RG, Wozney JM. Augmentation of alveolar bone and dental implant osseointegration: clinical implications of studies with rhBMP-2. J Bone Joint Surg Am. 2001;83-A(Suppl 1):S136.
18. Smolka W, Eggensperger N, Kollar A, Iizuka T. Midfacial reconstruction using calvarial split bone grafts. Arch Otolaryngol Head Neck Surg. 2005;131:131.
19. Jung RE, Windisch SI, Eggenschwiler AM, Thoma DS, Weber FE, Hämmerle CHF. A randomized-controlled clinical trial evaluating clinical and radiological outcomes after 3 and 5 years of dental implants placed in bone regenerated by means of GBR techniques with or without the addition of BMP-2. Clin Oral Implants Res. 2009;20:660.
20. Boyne PJ. Animal studies of the application of rhBMP-2 in maxillofacial reconstruction. Bone. 1996;19:83.
21. Davies SD, Ochs MW. Bone morphogenetic proteins in craniomaxillofacial surgery. Oral Maxillofac Surg Clin North Am. 2010;22:17.
22. Bachelet J-T, Bourlet J, Chateau J, Jacquemart M, Dufour C, Mojallal A, Gleizal A. Costal grafting in mandibular reconstruction. Plast Reconstr Surg Glob Open. 2015;3:e565.
23. Skovrlj B, Marquez-Lara A, Guzman JZ, Qureshi SA. A review of the current published spinal literature regarding bone morphogenetic protein-2: an insight into potential bias. Curr Rev Musculoskelet Med. 2014;7:182.
24. Shah MM, Smyth MD, Woo AS. Adverse facial edema associated with off-label use of recombinant human bone morphogenetic protein–2 in cranial reconstruction for craniosynostosis. J Neurosurg Pediatr. 2008;1:255.
25. Balaji SM. Use of recombinant human bone morphogenetic protein (rhBMP-2) in reconstruction of maxillary alveolar clefts. J Maxillofac Oral Surg. 2009;8:211.
26. Leal CT, Calvo AM, de Souza Faco RA, de Cunha Basto Júnior JC, Yaedú RY, da Silva Dalben G, Carvalho RM. Evolution of postoperative edema in alveolar graft performed with bone morphogenetic protein (rhBMP-2). Cleft Palate Craniofac J. 2015;52(5):e168–75. https://doi.org/10.1597/14-169.
27. Ribeiro Filho SA, Francischone CE, De Oliveira JC, Ribeiro LZ, Do Prado FZX, Sotto-Maior BS. Bone augmentation of the atrophic anterior maxilla for dental implants using rhBMP-2 and titanium mesh: histological and tomographic analysis. Int J Oral Maxillofac Surg. 2015;44:1492.
28. Moghadam HG, Urist MR, Sandor GKB, Clokie CML. Successful mandibular reconstruction using a BMP bioimplant. J Craniofac Surg. 2001;12:119.
29. Boyne PJ, Nakamura A, Shabahang S. Evaluation of the long-term effect of function on rhBMP-2 regenerated hemimandibulectomy defects. Br J Oral Maxillofac Surg. 1999;37:344.
30. Oral Maxillofacial Surgery, Medtronic INFUSE® Bone Graft. http://www.infusebonegraft.com/healthcare-providers/oral-maxillofacial-surgery/index.htm. Accessed 17 Jan 2018.
31. FDA Warning for Infuse Bone Graft Risks in Kids. https://www.schmidtlaw.com/fda-warning-for-infuse-bone-graft-risks-in-kids/. Accessed 17 Jan 2018.
32. Stiel N, Hissnauer TN, Rupprecht M, Babin K, Schlickewei CW, Rueger JM, Stuecker R, Spiro AS. Evaluation of complications associated with off-label use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in pediatric orthopaedics. J Mater Sci Mater Med. 2016;27:184.
33. Oetgen ME, Richards BS. Complications associated with the use of bone morphogenetic protein in pediatric patients. J Pediatr Orthop. 2010;30:192.