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SPECIAL TOPIC

Safety and Efficacy of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) in Craniofacial Surgery

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Introduction: Recombinant human bone morphogenetic protein-2 (rhBMP-2) is one of the most commonly used osteogenic agents in the craniofacial skeleton. This study reviews the safety and efficacy of rhBMP-2 as applied to craniofacial reconstruction and assesses the level of scientific evidence currently available.

Methods: An extensive literature search was conducted. Randomized controlled trials (RCTs), case series and reports in the English language as well as Food and Drug Administration reports were reviewed. Studies were graded using the Oxford Center for Evidence-Based Medicine Levels of Evidence Scale. Data heterogeneity precluded quantitative analysis.

Results: Seventeen RCTs (Levels of evidence: Ib-IIb) were identified evaluating the use of rhBMP-2 in maxillary sinus, alveolar ridge, alveolar cleft, or cranial defect reconstruction (sample size: 7–160; age: 8–75 years). Study designs varied in rigor, with follow-up ranging 3–36 months, and outcome assessment relying on clinical exam, radiology, and/or histology. There was wide variation in rhBMP-2 concentrations, carriers, and controls. Most studies evaluating rhBMP-2 for cranial defect closure, mandibular reconstruction, or distraction osteogenesis consisted of retrospective cohorts and case reports. The evidence fails to support RhBMP-2 use in maxillary sinus wall augmentation, calvarial reconstruction, mandibular reconstruction, or distraction osteogenesis. RhBMP-2 may be effective in alveolar reconstruction in adults, but is associated with increased postoperative edema.

Conclusions: A risk–benefit ratio favoring rhBMP-2 over alternative substitutes remains to be demonstrated for most applications in plastic and reconstructive surgery. Long-term data on craniofacial growth is lacking, and using rhBMP-2 in patients younger than 18 years remains off-label. *(Plast Reconstr Surg Glob Open 2019;7:e2347; doi: 10.1097/GOX.0000000000002347; Published online 19 August 2019.)*

INTRODUCTION

Bone morphogenetic protein (BMP) was introduced into clinical practice as a potential substitute to autogenous bone grafting and gained wide early adoption. Although it remains one of the most commonly used osteogenic agents in the craniofacial skeleton, a number of adverse events have been reported.[1,2] Urist[3] stimulated interest in BMP when he reported successful heterotopic bone formation in intramuscularly implanted demineralized bone matrix, driving investigations into the osteoinductive role of BMP and its potential clinical applications.[4] Over 20 types of BMP have since been described. They are members of the transforming growth factor beta superfamily and several have osteoinductive properties, most notably BMP-2 and BMP-7.[5–7] The sequencing and cloning of BMP genes in the 1990s made their mass production possible.[8] Recombinant human BMP-2 (rhBMP-2) and rhBMP-7 were the first to be introduced as bone graft substitutes, and rhBMP-2 remains the predominant BMP in clinical use today.

In 2002, rhBMP-2 (INFUSE; Medtronic, Memphis, Tenn.) was approved by the US Food and Drug Administration (FDA) for limited applications in

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Received for publication May 19, 2019; accepted May 29, 2019.

DOI: 10.1097/GOX.0000000000002347

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

single-level anterior lumbar interbody fusion.[9] FDA-approved indications subsequently expanded in 2004 to include the treatment of acute open tibial fractures,[10] and in 2007, rhBMP-2 was approved as an alternative to autogenous bone grafting for sinus and localized alveolar ridge augmentation.[11]

RhBMPs rapidly gained popularity; from 2002 to 2006, their use increased from 0.7% to 25% of all spine fusion procedures in the United States alone, with 85% of rhBMP use involving off-label applications.[12,13] RhBMPs initially favorable safety profile was soon overshadowed by concern regarding complications associated with ectopic bone formation, osteolytic defects, carcinogenesis, wound complications, and in cases of anterior cervical spine use, severe soft tissue swelling, dysphagia, and respiratory compromise.[1,2] This culminated in the issuance of a Public Health Notification by the FDA in 2008 alerting practitioners to those potentially life-threatening adverse events.[14] Despite its cost and risk profile,[15,16] rhBMP-2 continues to be used in various anatomical locations for FDA-approved and off-label applications. In contrast, rhBMP-7 (OP-1; Stryker Corporation, Kalamazoo, Mich.), which had initially received limited FDA approval under a Humanitarian Device Exemption for treatment of recalcitrant tibial nonunions, failed to gain FDA Premarket Approval in 2009 and its sales were eventually discontinued.[17] This review thus focuses on the current use of rhBMP-2, with particular emphasis on its safety and efficacy in craniofacial applications.

METHODS

An extensive literature search was conducted in PubMed and the Cochrane Library by 2 independent reviewers (E.P.R. and A.R.A.), using the terms "bone morphogenetic protein," "bone morphogenic protein," "recombinant human bone morphogenetic protein," "BMP," "BMP-2," "rhBMP-2." Titles, abstracts, texts, and references were reviewed. Systematic reviews, randomized controlled trials (RCTs), prospective or retrospective case series, and case reports in the English language were included. Animal studies were excluded, as were clinical studies outside the craniofacial skeleton. Relevant publically available FDA reports were reviewed. Studies were independently graded by 3 authors (E.P.R.; A.R.A.; and R.S.K.) using the Oxford Center for Evidence-Based Medicine Levels of Evidence Scale. Any discrepancy was resolved by discussion.[18] Data heterogeneity precluded a quantitative analysis.

RESULTS

Seventeen RCTs [levels of evidence (LOEs): Ib-IIb] were identified (Sample size: 7–160; age: 8–75 years), including 5 evaluating the use of rhBMP-2 in maxillary sinus floor augmentation, 7 in localized alveolar ridge augmentation, 4 in alveolar cleft reconstruction (Table 1), and one in cranial defect closure (Table 2). Study designs varied in methodology and analysis, with follow-up ranging from 3 to 36 months, and outcome assessment relying on various combinations of clinical exam, plain radiography, computerized tomography (CT), and/or histologic evaluation. There was wide variation in rhBMP-2 concentrations (0.05–1.5 mg/mL) and carriers [Absorbable collagen sponge (ACS) ± bovine bone xenograft (Bio-Oss), Bio-Oss alone, biphasic calcium phosphate, hydroxyapatite granules, β-Tricalcium phosphate/hydroxyapatite (β-TCP/HA), demineralized bone matrix, or hydrogel). Similarly, a variety of controls were used (autogenous bone graft ± allograft, Bio-Oss, ACS, β-TCP/HA, DBM, periosteoplasty, or no treatment). Systematic reviews and meta-analyses were significantly limited by the heterogeneity of the studies included, their lack of power, risk of bias, and inconsistent reporting of adverse events.[49–51] The most notable side effect was prolonged severe edema. No statistically significant increase in infection, heterotopic ossification, malignant transformation, or airway compromise was found in studies evaluating the use of rhBMP-2 in craniofacial surgery.

Five RCTs evaluated rhBMP-2 in maxillary sinus floor augmentation (n = 22–160; age ≥ 18 years) (Table 1).[19–23] Two multicenter RCTs with 24–36 months follow-up compared rhBMP-2 to bone auto ± allograft controls and found equivalent histology but superior bone formation on CT and more successful implant placement and functional loading in the control groups.[19,20] Three RCTs compared rhBMP-2 on different carriers to xenograft controls with varying results: a multicenter RCT reported significantly higher bone formation with rhBMP-2 based on histomorphometry at 3 months.[23] A smaller study favored the xenograft control group on histomorphometry at 9 months.[21] A multicenter RCT by Kim et al[22] reported radiological and histological equivalence between rhBMP-2 and xenograft controls. Facial edema lasting up to 5 weeks with rhBMP-2 was reported in 3 of the 5 trials.

Seven RCTs evaluated rhBMP-2 in alveolar ridge augmentation (n = 11–80; age ≥ 18 years) (Table 1).[24–30] One single-center trial compared rhBMP-2 with mandibular autogenous bone graft and found no significant difference in bone formation using an analog caliper and cone-beam CT.[27] Four studies favored rhBMP-2 over various controls including Bio-Oss, ACS, β-TCP/HA, or no treatment, using direct measurement, CT imaging, and/or histology.[24–26,28] Two studies found no significant difference between rhBMP-2 and DBM or Bio-Oss controls.[29,30] Facial edema lasting up to 2 weeks was more frequent and severe with rhBMP-2 exposure.

Of 4 RCTs comparing rhBMP-2 to iliac crest bone graft (ICBG) in alveolar cleft reconstruction (n = 7–21; age 8–16 years) (Table 1),[31–34] the only trial with results favoring rhBMP-2 enrolled skeletally mature patients only (mean age 16 years).[31] The study reported significantly higher estimated graft take in the rhBMP-2 group on intraoral examination, better bone healing, enhanced mineralization, and relative alveolar defect filling on Panorex and three-dimensional CT scans. Other trials included younger or skeletally immature participants; 2 trials reported equivalence between rhBMP-2 and ICBG controls on CT, while one favored ICBG controls.[32–34] Severe orofacial edema was reported, occasionally resulting in wound dehiscence.

Table 1. Randomized Controlled Trials on the Use of rhBMP-2 in Maxillary Sinus, Alveolar Ridge, and Alveolar Cleft Reconstruction

Clinical Application	References	Methodology	LOE	n	Age (y)	FU (mo)	Comparison	Efficacy (Bone Formation)	Adverse Events (rhBMP-2-related)
Maxillary sinus augmentation	Boyne et al[19]	PB-RCT (multicenter)	Ib	48	≥18	36	rhBMP-2 (0.75 mg/mL) + ACS versus rhBMP-2 (1.50 mg/mL) + ACS versus bone graft (auto ± allograft)	Favors control	Edema (dose dependent)
	Triplett et al[20]	P-RCT (multicenter)	IIb	160	≥18	24	rhBMP-2 (1.5 mg/mL) + ACS versus bone graft (auto ± allograft)	Favors control	Edema
	Kao et al[21]	P-RCT (number of centers NR)	IIb	22	≥18	9	rhBMP-2 (1.5 mg/mL) +ACS + Bio-Oss versus Bio-Oss alone	Favors control	None
	Kim et al[22]	PB-RCT (multicenter)	Ib	46	>18	6	rhBMP-2 (1.5 mg/mL) + BCP versus Bio-Oss	No difference	None
	Kim et al[23]	PB-RCT (multicenter)	Ib	147	>18	3	rhBMP-2 (1 mg/mL) + hydroxyapatite vs Bio-Oss	Favors rhBMP-2	Edema (2–5 weeks)
Alveolar ridge augmentation	Jung et al[24]	PB-RCT (single center)	Ib	11	27–75	6	rhBMP-2 (0.5 mg/mL) + Bio-Oss versus Bio-Oss	Favors rhBMP-2	None
	Fiorellini et al[25]	PB-RCT (multicenter)	Ib	80	47.4 (mean)	4	rhBMP-2 (0.75 mg/mL) + ACS versus rhBMP-2 (1.50 mg/mL) + ACS versus ACS alone versus no treatment	Favors rhBMP-2 (dose dependent)	Edema, erythema
	Huh et al[26]	PB-RCT (multicenter)	Ib	72	35–65	3	rhBMP-2 (1.5 mg/mL) + β-TCP/HA versus β-TCP/HA	Favors rhBMP-2	None
	De Freitas et al[27]	P-RCT (single center)	IIb	24	≥18	6	rhBMP-2 (1.5mg/mL) + ACS versus mandibular autogenous bone graft	No difference	Edema (2 weeks)
	Coomes et al[28]	P-RCT (single center)	IIb	39	≥18	5	rhBMP-2 (1.5 mg/mL) + ACS versus ACS	Favors rhBMP-2	Edema, erythema (10 d)
	Kim et al[29]	PB-RCT (multicenter)	IIb	69	20–70	3	rhBMP-2 (0.05 mg/mL) + DBM gel versus DBM	No difference	None
	Nam et al[30]	PB-RCT (single center)	IIb	17	20–68	4	rhBMP-2 (1mg/mL) + hydroxyapatite versus Bio-Oss	No difference	Edema
Alveolar cleft	Dickinson et al[31]	PB-RCT (single center)	IIb	21	16 (mean)	12	rhBMP-2 (1.5 mg/ml) + ACS versus ICBG	Favors rhBMP-2	None
	Alonso et al[32]	PB-RCT (single center)	IIb	16	8–12	12	rhBMP-2 (1.5 mg/mL) + ACS versus ICBG	Favors control	Edema (in 37% of rhBMP-2 group)
	Canan et al[33]	P-RCT (single center)	IIb	18	8–15	12	rhBMP-2 (1.5 mg/mL) + ACS versus ICBG versus periosteoplasty	No difference between rhBMP-2 and ICBG; both superior to periosteoplasty	None
	Neovius et al[34]	P-RCT (single center)	IIb	7	9.9 (mean)	6	rhBMP-2 (0.05 mg/mL + hydrogel versus 0.25 mg/mL + hydrogel versus ICBG	No difference; dose-dependent response noted	Edema (2 weeks) in higher dose group with associated wound dehiscence

β-TCP/HA, β-Tricalcium phosphate and hydroxyapatite; B, blinded; BCP, biphasic calcium phosphate; DMB, demineralized bone matrix; FU: follow-up; NR, not reported; P, prospective.

Reports of rhBMP-2 use in cranial defect closure included one RCT, whereas retrospective cohorts and case reports constituted the bulk of the evidence on mandibular reconstruction (Table 2) and distraction osteogenesis (DO). Successful bone formation was inconsistently achieved in cranial defect reconstruction, but more reliable in mandibular reconstruction and DO. More than half of the studies evaluating mandibular reconstruction noted significant edema. Dosing was not consistently documented in studies with lower LOE.

In the pediatric population, edema was also the most notable complication, occasionally necessitating steroid treatment or reoperation for rhBMP-2 implant removal.[36] A retrospective series of patients treated for nontraumatic

Table 2. Studies Describing the Use of rhBMP-2 in Cranial and Mandibular Defect Reconstruction

Clinical Application	References	Indication	Methodology	LOE	n	Age (y)	FU (mo)	Intervention/Comparison	Conclusion	Adverse Events (rhBMP-2-related)
Cranial defect reconstruction	Arnander, 2006[35]	Remote postsurgical infection and frontal bone loss	Case report	IV	1	60	4	rhBMP-2 + heparin + bovine collagen + hyaluronic acid + fibrin + ICBG	Ossification observed (insufficient yield)	None
	Shah et al[36]	Metopic craniosynostosis	Case report	IV	1	2	0.5	rhBMP-2 + ACS (concentration NR)	rhBMP-2 implant removed at postoperative day 10	Generalized scalp and facial edema, requiring steroids, antibiotics, reoperation, rhBMP-2 implant removal
	Skogh et al[37]	Neurosurgical defects	P-RCT	IIb	12	45–69	6	rhBMP-2 + hydrogel versus hydrogel	rhBMP-2 not associated with enhanced bone growth	None
	Beidas et al[38]	Nontraumatic defects	Retrospective case series	IV	36	2–13	5–16	rhBMP-2 + ACS versus cranial bone shavings	rhBMP-2 increased defect closure	Postoperative fusion of a previously patent cranial suture (9.5% of rhBMP-2 group)
Mandibular defect reconstruction	Jung et al[24]	Edentulism	PB-RCT	IIb	6/11	27–75	6	rhBMP-2 + ACS + Bio-Oss versus ACS + Bio-Oss	rhBMP-2 enhanced maturation of the regenerated bone	None
	Carter et al[39]	Trauma; nonunion; osteomyelitis; dentigerous cyst	Retrospective case series	IV	5	41–81	≤22	rhBMP-2 + ACS ± bone marrow cells and allogeneic cancellous bone chips	Restoration of the defect in 3/5 pts. Failures successfully treated with ICBG	Edema, nonunion, absence of bone regeneration, hardware failure
	Herford and Boyne[40]	Neoplasia; osteomyelitis	Retrospective case series	IV	14	10	6–18	rhBMP-2 + ACS	Successful defect restoration and implant placement	Hardware exposure
	Balaji[41]	Cyst	Case report	IV	1	6	6	rhBMP-2 + ACS + rib graft (auogenous)	Successful defect restoration	Edema
	Herford and Cicciù[42]	Giant cell tumor	Case report	IV	1	25	6	rhBMP-2 + ACS	Successful defect restoration	NR
	Misch[43]	Mandibular atrophy	Retrospective case series	IV	5	NR	6	rhBMP-2 + ACS + allograft	Bone formation on CT, low density	Edema
	Sweeny et al[44]	Osteoradionecrosis	Retrospective case series	IV	17	55.5 (mean)	3–12	rhBMP-2 + ACS	No difference	No difference in malunion, reoperation, swelling, or infection
	Cicciù et al[45]	BRONJ	Retrospective case series	IV	17/20	NR	6–12	rhBMP-2 + ACS	Successful bone formation	NR
	Cicciù et al[46]	Ameloblastoma resection	Case report	IV	1	31	18	rhBMP-2 + ACS + DBM	Successful defect restoration	Edema
	Balaji[47]	Juvenile cemento-ossifying fibroma	Case report	IV	1	1.5	36	rhBMP-2 + ACS + rib graft (auogenous)	Successful defect restoration and implants placement	Edema
	Oliveira et al[48]	Osteosarcoma; osteomyelitis; hypoplasia/ failed distraction	Retrospective case series	IV	3	1–57	6–12	rhBMP-2 + ICBG or rhBMP-2 alone	Bone formation on CT	Edema

B, blinded; BRONJ, bisphosphonate-related osteonecrosis of the jaw; DMB, demineralized bone matrix; FU: follow-up; NR, not reported; P, prospective.

cranial defects reported postoperative fusion of previously patent cranial sutures in 9.5% of patients exposed to rhBMP-2.[38]

Of the 7 RCTs with results favoring rbmp-2, 5 (71%) reported no conflict of interest. One study did not include a disclosure statement, and one study reported funding by Medtronic. All 3 RCTs reporting equivalence between rhBMP-2 and autologous bone graft reported no conflict of interest.

DISCUSSION

RhBMP-2 Dosing and Carrier Scaffolds

Autologous bone graft is the treatment of choice for many defects of the craniofacial skeleton; however, bone graft has been associated with limited stock, absorption, donor site morbidity, and prolonged hospitalization. Bone substitutes and osteogenic agents such as hydroxyapatite, DBM, calcium phosphate-based synthetic materials, and BMP products have been proposed as potential therapies to circumvent the limitations of bone graft.[52,53] BMP has strong osteoinductive properties stimulating the proliferation, migration, and differentiation of mesenchymal stem cells into osteoblasts, and plays a role in regulating the expression of target genes involved in bone physiology.[5–7]

Dosing and carriers are important considerations for effective and safe BMP administration. Although ACS is most commonly used, the optimal rhBMP-2 carrier has yet to be established. Numerous biomaterials have been suggested, including natural or synthetic biodegradable polymers, inorganic materials, and composites.[54,55] Carriers that suboptimally bind BMP may result in its release into tissues at high concentration. Thus, the dose-dependent increase in bone formation is to be balanced with a greater potential for adverse events.[2,19,25]

Maxillary Sinus Wall Augmentation

The 5 RCTs evaluating rhBMP-2 in maxillary sinus floor augmentation were heterogeneous in design.[19–23] In 2 multicenter RCTs, efficacy was superior in the bone graft control group.[19,20] When xenograft was used as control, the only trial with results favoring rhBMP-2 had short follow-up and conclusions solely based on histologic parameters. Although facial edema lasting up to 5 postoperative weeks was reported, it did not result in airway compromise or dysphagia (Table 1). Boyne et al[19] found that patients treated with higher (1.50 mg/mL) rhBMP-2 concentrations had significantly greater edema than those receiving 0.75 mg/mL rhBMP-2 or bone grafting ($P < 0.05$), denoting a dose-dependent correlation with adverse events. RhBMP-2 therefore does not offer substantial clinical benefit as a bone substitute in maxillary sinus wall augmentation, and is associated with significant postoperative edema.

Alveolar Ridge Augmentation

Only one trial compared rhBMP-2 to autogenous bone graft in alveolar ridge augmentation and found no significant difference in bone formation. In other trials, rhBMP-2 was superior to ACS and β-TCP/HA, but not DBM. Two small trials compared rhBMP-2 on different carriers to xenograft controls with varying results (Table 1).[24–30] Most trials used CT to measure bone growth. All trials were limited by short follow-up (3–6 months). Severe postoperative edema was again reported with rhBMP-2. de Freitas et al[27] noted that recovery was twice longer for those patients, with edema preventing the use of a provisional prosthesis for 2 weeks postoperatively. The available evidence suggests that the efficacy of rhBMP-2 for alveolar ridge augmentation is superior to other bone substitutes and equivalent to bone graft, with the additional risk of prolonged postoperative edema.

Alveolar Cleft Reconstruction

RCTs investigating alveolar cleft reconstruction were the only ones to compare rhBMP-2 to bone graft controls in a craniofacial patient population below the age of 18 years. The only trial favoring rhBMP-2 over ICBG in terms of safety, efficacy, cost, and length of stay enrolled skeletally mature patients only.[31] Two additional trials including younger or skeletally immature participants reported equivalence between rhBMP-2 and ICBG. One RCT found results favoring ICBG.

Alonso et al[32,56] reported facial edema in 37% of patients exposed to rhBMP-2 without superior bone formation.[57] Results from a large retrospective series including 414 patients receiving rhBMP-2/DBM or ICBG corroborate those findings, with no statistical difference in the canine eruption rate or reoperative alveolar cleft repair.[58] No difference was found in major or overall complications. One patient exposed to rhBMP-2 required prolonged intubation for intraoperative airway swelling, but this was deemed unrelated to the agent. Patients exposed to rhBMP-2 had more local/wound complications including edema (14% versus 1.65%; $P < 0.0001$). One of them required outpatient steroid treatment, whereas others had spontaneous resolution; 4.6% had dehiscence with no additional intervention needed in half of the cases.[58]

The clinical data on the effect of rhBMP-2 on craniofacial growth are very limited. Studies by Alonso et al[54] and Raposo-Amaral et al[57,59] found no significant difference in nasal symmetry at 6 postoperative months, and no significant changes in upper lip and nostril anatomy or maxillary cephalometric proportions on three-dimensional CT at 1 year. Longer-term follow-up is lacking, and the studies had small sample sizes unequally randomized into rhBMP-2 and ICBG groups, with an even smaller number of patients undergoing imaging.

The evidence supporting the efficacy of rhBMP-2 in craniofacial bone formation is strongest in alveolar cleft reconstruction. However, in the absence of high-quality long-term data, the interaction of rhBMP-2 with skeletal growth remains to be elucidated. Caution is recommended as the use of rhBMP-2 in patients younger than 18 years of age remains off-label.

Calvarial Defect Reconstruction

Studies describing the use of rhBMP-2 in cranial defect reconstruction are included in Table 2. One RCT enrolled 12 patients (age range:45–69), comparing rhBMP-2 on

hyaluronan-based hydrogel to controls for standardized critical-size cranial defects resulting from neurosurgery.[37] For each patient in the treatment group, 4 craniotomy holes were treated with rhBMP-2/hydrogel (0.25 mg/mL), hydrogel alone, Spongostan (Ethicon) alone, or Tisseel (Baxter) mixed with bone autograft. In the control group, the holes were treated with Spongostan or Tisseel mixed with bone autograft. Bone healing was assessed with CT at 3–6 months. Comparing rhBMP-2/hydrogel to hydrogel alone without taking borehole location into account initially indicated somewhat superior healing with rhBMP-2, but a deeper analysis showed that this effect was confounded by a generally superior healing capacity in frontal compared to parietal-temporal bone, a finding that the study could not further investigate. No local or systemic adverse events were noted.

In a retrospective multicenter study including pediatric patients (age 2–13), Beidas et al[38] found that compared to cranial bone shavings alone, bone graft with rhBMP-2/ACS resulted in increased closure of cranial defects. However, there was postoperative complete fusion of previously patent cranial sutures in 9.5% of patients exposed to rhBMP-2.[38] Shah et al[36] used rhBMP-2 with fronto-orbital advancement in a 2-year-old with metopic craniosynostosis. The patient developed generalized scalp, face, and anterior cervical edema albeit without evidence of airway compromise. He necessitated steroids and operative removal of the rhBMP-2 implants, with dramatic improvement in swelling. No signs of infection were noted and the adverse event was attributed to an immune-mediated response to rhBMP-2, consistent with the literature. Of note, studies have described transient elevation in antibodies to rhBMP-2 or its carrier in a small percentage of patients, often without clear clinical manifestations.[19,20] In summary, the evidence points against the use of rhBMP-2 for calvarial reconstruction due to uncertain efficacy and concern for major adverse events.

Mandibular Reconstruction

Jung et al[24] treated edentulous mandibles with xenogenic bone substitute with or without rhBMP-2 at test and control defects within the same jaw; rhBMP-2 was associated with enhanced bone maturation. One wound dehiscence occurred, with no other adverse events. Lower level evidence exists for the use of rhBMP-2 in mandibular trauma, nonunion, osteonecrosis, osteomyelitis, and tumor resection (Table 2).[39–48] Orofacial edema is again the most common adverse event. Other complications such as nonunion, absence of bone regeneration, or hardware failure are difficult to attribute to rhBMP-2 rather than the surgical reconstruction itself. In a case series by Carter et al,[39] 2 of 5 patients failed rhBMP-2 therapy but were successfully treated with ICBG. The LOE is low and insufficient to support the use of rhBMP-2 in mandibular reconstruction.

Distraction Osteogenesis

Carstens et al[60] treated a patient with Tessier VII facial cleft and Pruzansky III left mandibular hypoplasia. At 2 years of age, the patient underwent distraction of the rudimentary mandible, followed by filling of the resultant periosteal chamber with rhBMP-2/ACS 2 months later, with complete consolidation of the defect. Two years later, the child's growth prompted the need for a second DO procedure, which involved osteotomy and distraction of the regenerated mandibular bone, and a reapplication of rhBMP-2/ACS at that site. The newly regenerated bone was reported to be functionally stable with no notable histological abnormality. There were no local or systemic adverse events.[61]

Franco et al[62] used rhBMP-2 in a "rapid distraction protocol" in 3 neonates with Pierre Robin sequence and respiratory compromise, whereby bilateral mandibular osteotomies, intraoperative distraction, and rhBMP-2 application were performed during the same operation. The patients were extubated within 2 days, avoiding tracheostomy. One mandibular site necessitated subsequent rib grafting for nonunion. The authors argued that this technique offers the advantage of distracting the mandible to its final length at the time of placement of the distractor, avoiding the latency period and distraction interval, and thereby decreasing the number of days on mechanical ventilation, the overall hospital stay, and potential related complications.

Other studies have described successful use of rhBMP-2 in combination with DO for mandibular or maxillary alveolar ridge or cleft reconstruction despite failure of autogenous grafting, with good subsequent response of the reconstructed bone to tooth eruption, orthodontic movement, or implant placement.[63,64] Although initial reports seem encouraging, the efficacy and safety of rhBMP-2 in DO remain to be validated in large prospective series with longer-term follow-up.

Lessons Learned from the Use of rhBMP-2 in Spine and Orthopedic Surgery

The clinical experience with rhBMP-2 is richest in spine surgery.[1,2] With the initial increase in rhBMP-2 use in the years following its FDA approval, a series of reports surfaced describing adverse events including heterotopic ossification, osteolysis, inflammatory complications, and malignancy.[1,2] In the setting of cervical spine fusion, adverse events included retropharyngeal swelling, dysphagia, and respiratory compromise requiring postoperative intubation, tracheotomy, or surgical site drainage, prompting the issuance of a Public Health Notification by the FDA.[2,14] No convincing evidence of similar severe rhBMP-2-related adverse events has been found in our extensive review of the craniofacial literature.

Carragee et al[1] reviewed data from the original 13 industry-sponsored trials including 780 patients undergoing spine surgery with rhBMP-2. No rhBMP-2–associated adverse events had been reported in those publications. Comparative review of FDA documents and subsequent publications revealed significant inconsistencies, and the study concluded that the true estimate of adverse events associated with rhBMP-2 in spine fusion ranged 10%–50% depending on the surgical approach. Under the Yale University Open Data Access Project, patient-level data from the Medtronic-sponsored RCTs were obtained and reviewed by 2 independent teams, with meta-analyses pub-

lished in 2013.[65,66] Both studies found rhBMP-2-related adverse events to be higher than initially reported, suggesting possible methodological flaws and potential bias.

Particularly relevant to the field of craniofacial surgery is rhBMP-2s safety profile in the pediatric population. RhBMP-2 use in patients under the age of 18 continues to be off-label. Therefore, there is also a lack of pediatric dosing recommendations. The orthopedic literature has several accounts of the use of rhBMP-2 in pediatric spine and long bone surgery. The studies report edema, dehiscence, hematoma, compartment syndrome, infection, and the need for reoperation in cases where rhBMP-2 was used, but the rates are close to those generally cited for those procedures. The potential role of rhBMP-2 is difficult to elucidate given the lack of adequate control and limited follow-up.[67–74] Speculation on the long-term safety of rhBMP-2 continues, particularly regarding the risk of malignancy, with conflicting reports.[75–77] There is however some physiological basis to substantiate concerns as BMP-2 plays many roles at the cellular level, and deviation from its physiologic expression has been associated with tumors involving the prostate, breast, oral mucosa, pleura, and bone.[2] Additional high-quality long-term evidence is necessary to better assess the safety and efficacy of rhBMP-2 in adult and pediatric patients, and its long-term effect on craniofacial growth.

CONCLUSIONS

The safety profile of rhBMP-2 and the quality of evidence supporting its use are in development. The evidence does not support the use of RhBMP-2 in maxillary sinus wall augmentation and points against its use in calvarial reconstruction. There is insufficient evidence for the use of rhBMP-2 in mandibular reconstruction or DO. RhBMP-2 may be effective in alveolar ridge augmentation and alveolar cleft reconstruction in adults, but is associated with increased risk of postoperative edema. There is a lack of long-term data on craniofacial growth, and the use of rhBMP-2 in patients younger than 18 years of age remains off-label. A risk–benefit ratio favoring rhBMP-2 over alternative substitutes remains to be demonstrated for most applications relevant to plastic and reconstructive surgery.

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