Use of recombinant human Bone Morphogenetic Protein (rhBMP-2) in reconstruction of maxillary alveolar clefts

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Abstract

Background Use of rhBMP2 has been demonstrated to be an ideal bone reconstructive material for alveolar clefts. There is a lack of such studies from Indian cleft patients.

Aim To compare rhBMP2 alveolar cleft repair and iliac crest graft treated cases.

Materials and method Retrospective analysis of rhBMP2 alveolar cleft repair and iliac crest graft treated cases.

Predictor variables Gender, type of surgery and type of cleft

Outcome variables Total surgery time, blood loss at surgical and harvest site, length of scar, number of days on antibiotics, serratiopeptidase and NSAIDS; sutured days, number of days to regain masticatory functions, pain VAS on 5th postoperative day and at harvest site on a scale of 10; duration of edema, number of working days lost, time until child could walk 'normally'; mean efficiency of bone deposition.

Statistics Descriptive, paired 't' test, one way ANOVA

Results Difference between rhBMP2 and iliac crest graft treated cases in terms of antibiotic use, serratiopeptidase, NSAIDS, pain at surgical site, edema, number of working lost for attendees and number of days to walk unaided were statistically significant.

The mean length of surgery for unilateral cases was 87.60 minutes whereas it was 108.75 minutes for bilateral cases ($p=0.003$).

The mean efficiency of bone deposition as revealed loss in radiolucency for rhBMP2 treated cases was 91.74% whereas iliac crest graft cases showed a 87.96% ($p=0.006$).

Discussion It is evident that one has to reject null hypothesis in favor of the alternate hypothesis. The rhBMP2 is better than the conventional gold standard of iliac crest graft for restoration of maxillary alveolar clefts in terms of considered surgical, post surgical and radiographic planimetry parameters.

Conclusion Sparing children from the procedure of iliac crest harvesting is by itself a compelling reason to favor rhBMP2 use. It avoids the unnecessary surgery, loss of blood and postoperative morbidity of iliac crest harvesting.

Keywords rhBMP2 · Alveolar cleft

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Introduction

Boyne in 1974 advocated the use of autogenous iliac crest graft to repair alveolar cleft repair. When properly performed, the

outcomes are usually excellent [1]. This surgery has a significant morbidity associated with harvesting bone grafts from iliac crest besides pain, paraesthesia of lateral thigh and general anaesthesia complications.

These complications could be avoided if an iliac crest graft were avoided; the patient would undergo less trauma and risk. Hence a variety of alternatives including variety of grafts, graft substitutes were tried with

certain complications of their own including root resorption or graft dehiscence, remain osteoconductive (enhances bone formation) and require viable bone at periphery, which is often not available. These bones are not osteoinductive (initiates bone formation). Alloplastic materials such as hydroxyapatite impede normal tooth eruption, growth and orthodontic movements [1].

With the constraints associated with replacement material, search for completely synthetic bioimplants commenced. By the late 1980s, the active factor responsible for the induction of bone was identified: Bone Morphogenetic Protein (BMP). BMP replicates the embryonic induction of bone formation. It can induce pluripotent mesenchymal stem cells to differentiate into bone-forming osteoblasts. In the early 1990s, it became possible to fabricate these proteins synthetically using recombinant technology and, by 2006, this finally led to the development of OP-1 (BMP-7; Stryker Biotech, Hopkinton, Mass.) and Infuse (BMP-2; Medtronic, Fridley, Minn.), both of which are now available for clinical use [2].

BMP has been demonstrated to have osteoinductive properties [3,4]. With recent

approval of FDA, use of rhBMP2 has been indicated in for use in certain oral and maxillofacial bone grafting procedures, including sinus augmentation and localized alveolar ridge augmentation beside spine and fracture treatment [4]. Large scale studies using this technique and material had never been ventured in maxillary clefts or any similar defects in India. This retrospective study aims to compare the rhBMP2 alveolar cleft repair and the iliac crest graft treated cases.

Material and methods

Case history and follow up records of patients who had undergone non-syndromic cleft repair surgeries at this center in Chennai during January 2008–December 2008 (12 months) fulfilling the following criteria were included for the study.

1. All patients undergoing reconstruction of alveolar clefts with rhBMP2.
2. For comparing, age and type of cleft matched (± 1 year) cases iliac crest graft cases were retrieved from archives fulfilling following criteria.

3. A minimum of radiographic cleft area of 15 mm² area (in orthopantomogram) with a significant loss of clinical form, function and or esthetics.
4. Patients with a minimum of 4 months follow up with orthopantomograms.
5. Repeat or corrective surgeries of previous attempted surgeries were not included in the study.
6. Patient who did not have follow up for less than 4 months were excluded from the study.
7. Patients report's that did not have all data required for the study.

Age, gender, type (unilateral/bilateral), side of the defect, type of graft (rhBMP2 or iliac crest graft), total surgery time (in minutes); blood loss at surgical and harvest site—approximate measurement by the theatre assistant by calculating the difference in saline used and volume collected in suction apparatus and weight of cotton/gauze pieces during accounting of cotton/gauze at the end of surgery; length of scar—measured on the 4th month postoperative in millimeters; number of days on antibiotics, serratiopeptidase and NSAIDS; sutured days—number of days lapsed between surgery and removal of

Table 1 Type of non-syndromic cleft cases in both surgical modalities

Type of graft used	Bilateral n(%)	Unilateral left side n(%)	Unilateral right side n(%)	Total	P value
rhBMP2	6 (20)	14 (46.7)	10 (33.3)	30	0.959
Iliac crest graft	6 (20)	13 (43.3)	11 (36.7)	30	

Table 2 Type of non-syndromic cleft cases in both genders in both surgical modalities

Type of graft used	Males n (%)	Females n (%)	Total n (%)	P value
rhBMP2	10 (33.3)	20 (66.7)	30 (50)	0.5
Iliac crest graft	9 (30)	21 (70)	30 (50)	
Total	19 (31.7)	41 (68.3)	60 (100)	

Table 3 Descriptive statistics of surgical and post surgical parameters of the study group

Parameter	Minimum	Maximum	Mean	Standard Deviation
Total surgery time (in minutes)	60	150	91.83	22.76
Approximate blood loss from surgical site (in mL)	50	90	59.67	9.11
Approximate blood loss from harvest site (in mL)	0.00	90	35.67	36.62
Length of scar (in cms)	0.00	3.2	1.35	1.38
Antibiotic use (in days)	5	10	5.57	1.25
Seratopeptidase use (in days)	5	24	9.87	3.36
NSAIDS (in days)	3	24	7.72	4.2
Days taken for Suture removal at harvest site	0	10	3.88	4.05
Regain of Masticatory function – soft diet (in days)	1	3	2.18	0.57
Regain of masticatory function – regular diet (in days)	4	15	8.97	2.13
Pain (surgical site) in Visual analogue scale on 5 th post-operative day	1	5	2.05	1.05
Pain (harvest site) in Visual analogue scale on 5 th Post-operative day	0	5	1.47	1.68
Duration of edema (in days)	1	8	5.18	1.99
Number of working days lost for attendees	4	30	11.17	5.3
Days taken for patient to walk normally	1	4	1.9	0.92

non-resorbable sutures placed at surgical sites; number of days to regain masticatory functions (soft–number of days required to take semisolid or soft diet postoperatively; regular–number of days required to take regular diet postoperatively); pain VAS on the 5th postoperative day and pain at harvest site on a scale of 10; duration of edema, number of working days lost–refers to the average number of working days lost by the patient as well as the attendees and time until the child could walk ‘normally’.

Efficiency–radiographic planimetry from preoperative and 16 week postoperative orthopantomogram was used to measure the size of the defect. The size of the defect was traced on to a standard tracing sheet and the area involved was counted after laying it on to a regular graph sheet (with minimal marking of 1mmx1mm). One small square is 1mm². All the involved squares, with atleast 50% of involved area were taken into measurement as single mm² area. The procedure was repeated by 2 independent assistant surgeons beside the author. In case of discrepancy, the average of three values was taken as the final value. In postoperative

orthopantomograms, areas with definitive radiolucency were only considered. Efficiency of healing was calculated by as below:

(Preoperative radiolucency area – 4th month postoperative radiolucency area/ preoperative deficiency) *100

All the above data were entered and analyzed using Statistical Package for Social Service (SPSS) version 16.0. Descriptive statistics were provided for all the variables. Comparison of means (T-test) were performed and presented for predictor and variables. One way ANOVA was performed between efficiency and gender, side, age and type of surgical modality. A p-value of <0.05 was taken as significant.

Results

There were 32 cases of non-syndromic cleft repair involving the reconstruction of alveolus performed during this period at the centre with rhBMP2. Of this only 30 cases fulfilled the criteria and constituted the study group. The remaining 2 cases had

their radiographs and case histories were not retrievable. There were 30 age matched (± 1 year) and type of cleft matched iliac crest graft treated cases for comparison.

Of the 60, the mean age of patients was 8.26 ± 2.61 years and a median of 7.5 years. The age ranged from 1.5 years to 13 years. There were 41 females (68.3%) and 19 males (31.7%).

Of the total study group, 12 cases (20%) were bilateral cases. Of the remaining 48 unilateral cases, 27 cases (45%) had left side involvement and rest 21 cases (35%) were in the right side. There were 6 cases each in bilateral cases and 24 cases each in unilateral cases. The right: left side was (1:1.4)

Of all the cases in the study group, 30 cases (50%) had undergone rhBMP2 graft while the remaining cases were treated with iliac crest graft. Table 2 depicts the distribution of genders between the two types of surgeries. The difference was not statistically significant ($p=0.5$).

The mean age of patient's who underwent surgery with rhBMP2 was 8.24 ± 2.82 years while the mean age of patient who underwent surgery with iliac crest graft

Table 4 Comparison of means of surgical and post-surgical parameters between 2 surgical modalities by T test

Parameters	Type of Graft	Mean	Std. Deviation	P value
Total surgery time (in minutes)	rhBMP2	86.50	20.18	0.069
	iliac crest	97.17	24.24	
Approximate blood loss from surgical site (in mL)	rhBMP2	59.83	8.86	0.889
	iliac crest	59.50	9.50	
Approximate blood loss from harvest site (in mL)	rhBMP2	.00	.00	0.000
	iliac crest	71.33	9.82	
Length of scar (in cms)	rhBMP2	.00	.00	0.000
	iliac crest	2.71	.26	
Antibiotic use (in days)	rhBMP2	5.13	.63	0.006
	iliac crest	6.00	1.56	
Seratopeptidase use (in days)	rhBMP2	8.73	1.78	0.008
	iliac crest	11.00	4.14	
NSAIDS (in days)	rhBMP2	4.57	1.36	0.000
	iliac crest	10.87	3.68	
Days taken for suture removal at harvest site	rhBMP2	.00	.00	0.000
	iliac crest	7.77	1.48	
Regain of masticatory function – soft diet (in days)	rhBMP2	2.20	.56	0.822
	iliac crest	2.17	.6	
Regain of masticatory function – regular diet (in days)	rhBMP2	9.13	1.93	0.551
	iliac crest	8.80	2.36	
Pain (surgical site) in visual analogue scale on 5th postoperative day	rhBMP2	1.50	.86	0.000
	iliac crest	2.60	.93	
Pain (harvest site) in visual analogue scale on 5th postoperative day	rhBMP2	.00	.00	0.000
	iliac crest	2.93	1.14	
Duration of edema (in days)	rhBMP2	6.63	1.129	0.000
	iliac crest	3.73	1.55	
Number of working days lost for attendees	rhBMP2	8.73	2.53	0.000
	iliac crest	13.60	6.17	
Days taken for patient to walk normally	rhBMP2	1.20	.41	0.000
	iliac crest	2.60	.72	

Table 5 Comparison of means of surgical and post-surgical parameters between genders by T test

	Gender	Mean	Std. Deviation	P value
Total surgery time (in minutes)	female	95.37	23.14	0.077
	male	84.21	20.43	
Approximate blood loss from surgical site (in mL)	female	60.85	8.73	0.139
	male	57.11	9.62	
Approximate blood loss from harvest site (in mL)	female	37.2	37.37	0.639
	male	32.37	35.72	
Length of scar (in cms)	female	1.39	1.38	0.809
	male	1.29	1.42	
Antibiotic use (in days)	female	5.51	1.21	0.625
	male	5.68	1.38	
Seratopeptidase use (in days)	female	9.39	2.51	0.107
	male	10.9	4.63	
NSAIDS (in days)	female	7.98	4.63	0.488
	male	7.16	3.11	
Days taken for suture removal at harvest site	female	4.02	4.16	0.695
	male	3.58	3.9	
Regain of masticatory function – soft diet (in days)	female	2.2	.56	0.815
	male	2.16	.60	
Regain of masticatory function – regular diet (in days)	female	9.2	2.02	0.227
	male	8.47	2.4	
Pain (surgical site) in visual analogue scale on 5th postoperative day	female	2.1	1.02	0.610
	male	1.95	1.13	
Pain (harvest site) in visual analogue scale on 5th postoperative day	female	1.56	1.72	0.528
	male	1.26	1.63	
Duration of edema (in days)	female	5.17	2	0.943
	male	5.21	2.02	
Number of working days lost for attendees	female	11.37	5	0.672
	male	10.74	5.98	
Days taken for patient to walk normally	female	1.93	.93	0.742
	male	1.84	.9	

Graph 1 Simultaneous 95% confidence intervals for means

Reference line is the overall mean = 89.85

was 8.28 ± 2.42 years. There was no statistical difference between the mean of the ages ($p=0.961$).

Table 3 depicts the descriptive statistics of surgical and post surgical parameters of the study group. Table 4 shows the comparison of means of surgical

and post surgical parameters between 2 surgical modalities. The difference between rhBMP2 and iliac crest graft treated cases, in terms of antibiotic use, serratopeptidase, NSAIDS, pain at surgical site, edema duration, number of working lost for attendees and number of

days to walk unaided were statistically significant.

Table 5 depicts the comparison of means of surgical and post surgical parameters between genders. There was no statistically significant difference between genders in any of the considered parameters. Table 6 compares the means of surgical and post surgical parameters between bilateral and unilateral alveolar clefts. The mean length of surgery for unilateral cases was 87.60 minutes whereas it was 108.75 minutes for bilateral cases. This difference between mean lengths of surgery between the 2 types was statistically significant ($p=0.003$).

Table 7 shows the mean efficiency of bone deposition as revealed loss in radiolucency for both the surgical techniques, measured by one-way ANOVA. The mean efficiency of rhBMP2 treated cases was 91.74% whereas iliac crest graft used cases showed a 87.96%. This difference was statistically significant ($p=0.006$). This has been shown in graph 1.

The mean efficiency of bone deposition as revealed loss in radiolucency for genders and age, measured by one-way ANOVA, revealed that difference in mean efficiency

Table 6 Comparison of means of surgical and post-surgical parameters between 2 types of clefts by t-test

	Type of cleft	Mean	Std. Deviation	P value
Total surgery time (in minutes)	Bilateral	108.75	23.17	0.003
	Unilateral	87.60	20.81	
Approximate blood loss from surgical site (in mL)	Bilateral	71.25	10.69	.000
	Unilateral	56.77	5.88	
Approximate blood loss from harvest site (in mL)	Bilateral	43.33	45.34	0.422
	Unilateral	33.75	34.40	
Length of scar (in cms)	Bilateral	1.31	1.37	0.901
	Unilateral	1.37	1.39	
Antibiotic use (in days)	Bilateral	5.25	0.87	0.332
	Unilateral	5.65	1.33	
Seratopeptidase use (in days)	Bilateral	10.50	4.54	0.47
	Unilateral	9.71	3.04	
NSAIDS (in days)	Bilateral	7.08	3.26	0.564
	Unilateral	7.88	4.42	
Days taken for suture removal at harvest site	Bilateral	4.08	4.38	0.85
	Unilateral	3.83	4.01	
Regain of masticatory function – soft diet (in days)	Bilateral	2.25	.62	0.65
	Unilateral	2.17	.56	
Regain of masticatory function – regular diet (in days)	Bilateral	9.58	1	0.268
	Unilateral	8.81	2.32	
Pain (surgical site) in visual analogue scale on 5th postoperative day	Bilateral	2.17	1.34	0.67
	Unilateral	2.02	0.98	
Pain (harvest site) in visual analogue scale on 5th postoperative day	Bilateral	1.17	1.47	0.494
	Unilateral	1.54	1.74	
Duration of edema (in days)	Bilateral	5.00	2.05	0.724
	Unilateral	5.23	2.0	
Number of working days lost for attendees	Bilateral	12.92	7.32	0.202
	Unilateral	10.73	4.64	
Days taken for patient to walk normally	Bilateral	2.084	1.08	0.442
	Unilateral	1.85	.88	

Table 7 Comparison of mean efficiency percentage of radiographic obliteration of cleft by surgical techniques using one-way ANOVA

	Mean efficiency (in %)	Std. Deviation	95% Confidence interval for mean		Minimum (%)	Maximum (%)	P value
			Lower	Upper			
rhBMP2 group	91.74	3.69	90.37	93.12	84.38	98.24	0.006
Iliac crest group	87.96	6.27	85.61	90.3	68.55	97.18	
Total	89.85	5.45	88.44	91.26	68.55	98.24	

was not statistically significant in both conditions ($p=0.493$ and 0.745 respectively).

Discussion

The standard procedure for closure of maxillary alveolar cleft is using autogenous marrow from iliac crest graft. This procedure is accompanied by a substantial complication and significant morbidity. The harvesting procedure is a second surgical procedure performed concomitantly. There is a resultant scar at iliac crest, longer duration of anesthesia, pain on mobility in the iliac area, loss of blood and much more potential complication arising out of this procedure [1].

Wozney et al. sequenced rhBMP2, in 1989 and cloned it. This allowed production of large, pure quantities that can be used clinically and in the laboratory. This led to a host of research that translated into clinical studies involving spine fusions and long bone non-unions. These studies demonstrated efficacy and safety for human use. At the host site, it acts in-situ to concentrate host stem cells at the surgical site and differentiates them into osteoblasts [1]. This process recapitulates all of the events occurring during embryological bone formation and thus leads to formation of a normal, self bone in required quantity and quality [5,6]. rhBMP2 is available commercially and indicated for alveolar cleft repair procedures very recently. Long

terms follow up and success rate of this material is sparse in English literature [1].

Two-dimensional radiographs are usually used in the evaluation of secondary bone grafting for clefts, but these might sometimes contain inherent distortion factors. Computed Tomograms (CTs) might be a better alternative to provide a more accurate assessment. The problems with the use of CT include higher cost, increased radiation exposure, patient inconvenience, and accessibility. However, the information derived from the three-dimensional analysis could be advantageous excluding image enlargement and distortion, superimposition of adjacent structures, a limited number of identifiable landmarks, and positioning problems, all of which can

Preoperative view of the cleft

Freeze dried rhBMP-2 graft reconstituted with sterile saline bound to ACS graft

Postoperative view of the cleft-case treated with rhBMP2

Preoperative orthopantomogram

Postoperative orthopantomogram

Preoperative CT

Postoperative CT of rhBMP2 treated cases

Preoperative CT

Postoperative CT of rhBMP2 treated cases

adversely affect the quality of the images [8]. CT allows only 2 dimensional mapping whereas the orthopantomogram will allow a 3D volumetric analysis. But considering the cost and radiographic exposure, orthopantomograms are better modality to study the efficiency of bone formation as early as 4th month [3]. Planimetry has been used earlier to identify the efficiency rhBMP2 for healing in long bones [5]. However the approach used in the present study is quantitative than qualitative and gives a better approach to the question.

The difference between the cases in 2 surgical modalities and type of clefts ($p=0.959$), gender ($p=0.5$), mean age ($p=0.961$), with no statistical significance. This indicates that the distribution of cases between the 2 surgical modalities is not significant in spite of minor differences.

From tables 4, 5, 6 it is evident that the outcomes of surgical and post surgical parameters are influenced by the type of surgical modality with a high statistical significance rather than the gender or the type of cleft deformity.

Graph 5 lists the radiographic obliteration of the defect efficiency percentage for the entire study group. Graph 4 lists the mean difference of efficiency percentage between 2 surgical modalities with 95% confidence interval. As depicted in Table 7, rhBMP2 group has higher mean efficiency percentage as compared to the iliac crest group with a high statistical significance of $p = 0.006$. In a study by Chin et al. 2005 [1] satisfactory radiographic bone formations was observed in 3 months itself even for severe cleft deformities with a good consolidation. Loss of radiolucency is good evidence for consolidation of the defect. Similar successful studies in animals and the use of rhBMP-2/ACS in humans for maxillary sinus floor augmentation and alveolar ridge augmentation in a 16-week open-label feasibility study for maxillary floor sinus augmentation used 1.77–3.4 mg rhBMP-2 implanted in ACS. In this study, CT scans, in few cases, showed significant new bone growth (mean height 8.51 mm) in all evaluable patients and allowed the placement of dental implants [8].

Regain of masticatory function for both soft and regular diet was comparatively late and duration for edema was increased for rhBMP2 cases because it is reported that diffuse soft tissue swelling in the postoperative period at the surgical site is not unusual with rhBMP2 use and the cause of this phenomenon is unknown. However it is believed that an exaggerated inflammatory reaction is likely responsible for both the success in promoting bone formation as well as the adverse effect of soft-tissue swelling. This may very well be a dose-dependent phenomenon that still needs to be investigated for future use of rhBMP2 [9,10]. On contrast, pain in surgical site on a visual analog scale on 5th postoperative day at surgical site was significant as inflammatory mediators rush to surgical site owing to the inflammatory response to rhBMP2.

Statistically significant difference in the efficiency of the surgical modalities clearly

indicates that surgery with rhBMP2 has a better bone formation as indicated by obliteration of radiolucency in orthopantomograms. The results were similar to a 3 dimensional studies volumetric studies in alveolus clefts by Herford AS et al. [11] and Dickinson BP et al. [12]

It is reported that in spine surgeries, rhBMP2 use, as compared to autogenous iliac crest graft, reduced operating room and anesthesia time by 30 minutes, reduced recovery room time by 15 minutes, lost less blood, reduced probability of transfusion, autograft extenders and harvesters. rhBMP2 reduced length of stay by 0.5 days. Our findings are consistent with these by Polly DW et al. [13], in spine surgeries. Reported over all complication rates for autogenous iliac crest graft range from 15% to 49%. Incidence of major complication range from 2 to 39% while minor complication range from 2% to 39%. This complications included donor site pain, infection, hematoma, dehiscence, vascular injuries and iliac crest fracture. Literature reports of a iliac crest fracture rate of 3.7–4%. 4–10% of patients reported hematoma. Donor site pain, a common complication of autogenous iliac crest bone graft has no known exact etiology. The suggested causes include direct nerve injury, sacroiliac joint violation, sharp edges at harvest site and a part of generalized pain syndrome. They reported a visual analog scale of 6–7 after 1 month at the donor site [13]. It shall be remembered that the amount of graft required for spinal surgeries exceed by atleast 2 folds for cleft surgeries, depending on the size of the defect.

Bone harvest time from iliac crest takes a variable time of 30–45 minutes, with shortest time being reported as 20 minutes [13]. With use of rhBMP2, its need is completely avoided.

Furthermore studies done on rhBMP2 treatment in spine, preliminary results suggest that from a payer perspective, the upfront price of rhBMP2 is likely to be entirely offset by reductions in the use of other medical resources. That is, rhBMP2 appears to be cost neutral. The cost offsets were attributable largely to prevention of pain and complications associated with autogenous iliac crest bone graft, as well as reduction of the costs associated with fusion failures [14].

Considering the above discussion, it is evident that one has to reject the null hypothesis in favor of the alternate hypothesis. The rhBMP2 is better than the

conventional gold standard of iliac crest graft for restoration of maxillary alveolar clefts in terms of considered surgical, post surgical and radiographic planimetry parameters.

Conclusion

This study clearly indicates that there is an obvious advantage of rhBMP2 use over iliac crest bone in terms of surgical, post surgical recovery parameters and the efficiency of radiographic obliteration of the defect. Sparing children from the procedure of iliac crest harvesting is by itself a compelling reason to favor rhBMP2 use. It avoids the unnecessary surgery, loss of blood and postoperative morbidity of iliac crest harvesting. Furthermore the presence of scar is objectionable in case of females. The efficacy of the material in establishing an osseous union for the alveolar discontinuity was clear. As the surgical procedure of alveolar cleft repair using this material involves only oral mucosa manipulation, it is possible in distant future that patients would tolerate this kind of surgeries without the need for general anesthesia. Such an alveolar repair may provide access to surgeries even at areas where facilities for general anesthesia may be limited. Limited displacement of rhBMP2 into adjacent tissue may form ectopic bone formation or affect nerves coming into account with rhBMP2. However no such effects were observed in oro-facial literature or evidence found in our study. The long term effects of this surgery have to be observed over a period of time.

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