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Efficacy of iranian-made bone substitutes for regeneration of rabbit calvarial bone defects: cenobone versus the ITB

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ABSTRACT

Introduction: Efforts are being made to improve the efficacy of biomaterials used as bone substitutes for bone regeneration in the oral and maxillofacial region. Graft materials have been recently produced in Iran; however, studies are required to confirm their efficacy. This study aimed to compare the histomorphometric results of using mineralized allografts produced by the Hamanandsaz Baft Kish Company and the Iranian Tissue Bank (ITB) for regeneration of rabbit calvarial bone defects.

Materials and Methods: In this animal study, four similar holes with a minimum diameter of 6.5 mm were created in the calvaria of 14 white New Zealand rabbits. The defects were filled with Cenobone (Hamanandsaz Baft Kish Co.), ITB product and Cerabone (Botiss Co). One defect remained unfilled as the control group. One and two months after implantation, the animals were sacrificed and the defects was subjected to histologic and histomorphometric assessments. The amount of new bone formation and the volume of remaining biomaterials were analyzed using one-way ANOVA. The inflammatory reaction was analyzed by the Kruskal Wallis test and the foreign body reaction, bone quality and bone-graft interface pattern were analyzed using the Fisher's exact test.

Results: The amount of new bone formation was 0.060.1± and 0.11± 0.1, 0.040.08± and 0.110.09±, and 0.080.12± and 0.090.06± mm2 in the ITB, Cerabone and Cenobone groups at one and two months post-implantation, respectively.

The effect of time and type of biomaterial on the amount of new bone formation was not significant. At one month, significant differences were seen in the amount of remaining biomaterials in the defects among the three groups ($P<0.05$). The highest amount of remaining biomaterial was noted in the Cenobone and Cerabone groups. At two months, this difference was not statistically significant. At one month, moderate inflammation was noted in most defects and no difference was found among the groups ($P<0.04$). At two months, mild inflammation was observed in most defects with no statistically significant difference among them.

Conclusion: Bone allografts such as Cenobone and ITB had optimal efficacy for bone regeneration in rabbit calvarial defects comparable to that of Cerabone xenograft. Considering the limitations of in vitro studies, application of these biomaterials must be evaluated in clinical studies.

Keywords: Bone formation, Cenobone, Cerabone, Calvarial defects.

Introduction

Bone healing process is complex and multifactorial. Several solutions have been proposed for bone grafting, including the use of autografts, allografts and alloplastic materials. Autogenous bone harvested from the host has good regeneration ability, but bone harvesting is painful and is often associated with some complications.

In addition, the volume of the harvested bone is limited and it cannot be stored. The efficacy of graft materials for bone augmentation has been previously assessed with variable and sometimes contradictory results. In some cases, bone graft materials do not well adhere to the bony bed and bone resorption after transplantation is inevitable. In addition, the use of these substances often imposes high costs on patients [1].

Allografts such as freeze-dried bone allografts (FDBAs) and demineralized freeze-dried bone allografts (DFDBAs) have great osteogenic potential due to exposure to bone morphogenic proteins (BMPs).

The allogeneic bone products are biocompatible and have remodeling ability; thus, they are used in many surgical procedures. Also, most bone substitute materials are hydroxyapatite (HA)-based such as bovine HA or synthetically produced HA and all of them are resorbable.

Materials such as Cenobone are non-vital connecо tive tissue derived from human and are prepared by the proprietary processing method for preservation of the extracellular matrix. This matrix serves as a scaffold for fibroblasts, blood vessels and the adjacent epithelium. The advantages of using Cenobone include the ability to maintain an ambient temperature, sterility, resorbability, maintaining the three-dimensionn al structure of bone, fast recovery, excellent clinical outcome, stimulation of bone formation, affordability and decreasing the operation time [3].

Sarkarat et al, in 2010 quantified alveolar ridge preservation and ossification after tooth extraction following the use of several graft materials. They found that foreign-made products (OSSEO +, American-made allograft) did not have any significant superiority to Cenobone [4]. The ITB company has produced a new product, which appears to be efficient for bone regeneration in maxillofacial defects.

On the other hand, replacement of the missing teeth with implants requires adequate quality and quantity of bone, which is not available in many patients.

The properties of autogenous bone allografts are closest to those of autografts, and the use of bone substitutes is valuable in some cases. This study aimed to compare the histomorphometric results of using a mineralized allograft manufactured by the Hamanandsaz Baft Kish company and the ITB for bone regeneration in rabbit calvarial defects.

Materials and Methods

This Case-control animal study was conducted on 14 white New Zealand rabbits with an average weight of 3 - 5.2 kg. animals were fed the same diet for one month prior to surgery. After surgical preparation, the animals were anesthetized by deep intramuscular injections of 10% ketamine and 2% xylocaine.

The surgical site was scrubbed with 7%Betadine and shaved. Then, the surgical site was isolated and scrubbed again with 7% Betadine for five minuted. Using a# 15 scalpel, a 10 centimeter incision was made and subcutaneous tissues were retracted using a periosteal elevator. Then, four holes with the same size and diameter (at least 6.5 mm) were created using a trephine bur and low speed handpiece under external irrigation with nrmal saline.

Standardization of the holes was performed using anatomic landmarks. In the first animal, the first defect was filled Cenobone (Hamanandsaz Baft Kish company, Kish, Iran). The second defect was filled with ITB (graft material produced in Tehran University) and the third defect was filled with CeraBone (Xenograft, Botiss, Germany). The fourth cavity remained empty as the control group. In the next animals,allocation of materials to defects was changed in a clockwise manner to minimize the confounding factors related to the location of defects. A chart was created for each animal.

Biomaterials including Cerabone, Cenobone and ITB with a particle diameter of 500 microns were used to fill the defects. After application of the biomaterials, the periosteum was sutured with 4/0 vicryl sutures and the skin was also sutured with 4/0 nylon sutures. Animals were taken to a warm place for recovery with a temperature of 37 centigrade degree. After the operation , 0.1 ml ketoprofen 0.6 ml enrofloxac in were injected subcutaneously daily for five days for the control of pain and infection. The rabbits were randomly divided into two groups.

The animals were sacrificed by 2cc intravenous injection of sodium thiopental. After sacrificing the rabbits at four and eight weeks (six rabbits at each time point) the calvaria was separated from the skull with a saw.

The tissues were placed in paraffin and fixed in 10% buffered formalin for 48 hours and decalcified in a buffer solution containing 10%formic acid.

Paraffin-embedded tissue blocks were cut into 20 5-micron thick slices and stained with hematoxylin -eosin for evaluation under a light microt scope. The amount and type of new bone formation , the amount of remaining biomaterials, presence or absence of inflammation , foreign body reaction and the bone-biomaterial interface were assessed by a pathologist using an optical microscope. The pathologist was blinded to the group allocation of samples. Two-way ANOVA was used to assess the effect of time on the amount of ossification and the remaining biomaterials. One-way ANOVA was used to compare the variables among the three groups at one and two-month time points.

Dunnett T3 test was applied for pairwise comparison of groups in terms of the amount of remaining biomaterials. Degrees of inflammation (ordinal variable) was compared among the four groups using the nonparametric Kruskal-wallis test.

The Mann-whitney test was used for pairwise comparisons. The Fisher›s exact test was used to assess the difference in distribution of variables such as foreign body reaction, bone quality and pattern of bone – graft biomaterial interface.

Results

The amount of new bone formation was 0.06±0.1 mm^2 and 0.11 ± 0.1 mm^2 in ITB group, 0.04 ± 0.08 mm^2 and 0.11 ± 0.09 mm^2 in Cerabone group, 0.05 ± 0.080 mm^2 and 0.05± 0.07 mm^2 in Cenobone group and 0.08 ± 0.12 mm^2 and 0.09 ± 0.06 mm^2 in the control group at one and two months, respectively.

Two-way ANOVA analyzed the effects of factors such as time (P=0.21) type of biomaterial (P=0.66) and also the interaction effect of time and type of biomaterial (P=0.65) on the amount of newly formed bone. The results were not statistically significant.

One-way ANOVA showed no significant difference in terms of the amount of regenerated bone between the first (P=0.84) and second months (P=0.44) following the application of biomaterials in rabbit calvarial defects.

Since there were no significant differences among the study groups, pairwise comparisons were not performed. On the other hand, one and two months following implantation of biomaterials, there were no significant differences in the amount of new bone formation in the ITB (P=0.33), Cerabone (P=0.18) , control (P=0.94) and Cenobone (P=0.93) groups (independent t-test).

At one month, moderate degree of inflammation had a higher frequency in the test groups (Table 1). Nonparametric Kruskal-Wallis test showed significant differences in the degree of inflammation in different biomaterial groups at one month after implantation ($p<0.04$). At two months, most groups showed signs of mild inflammation. The most severe inflammatory reactions were observed in the Cerabone group (Botiss) while the least inflammatory reactions were recorded in Cenobone group (Table 1).

Based on the nonparametric Kruskal-Wallis tast, at two months after implantation, no significant differences in levels of inflammatory reactions were noted among the groups ($p=0.23$)

In addition, comparison of the degree of inflammation in the first and second months after biomaterial implantation by the Mann-Whitney U test showed significant differences in ITB ($p<0.007$) and Cenobone ($p<0.02$) groups, but the difference in this regard in Cerabone ($p=0.46$) and control ($p=0.62$) groups was not statistically significant. According to the results of this study, at one month, evidence of foreign body reaction was noted in six (7.85%), two (28.6%), one (14.3%) and six (85.7%) samples in the ITB, Cerabone, control and Cenobone groups, respectively. At two months foreign body reaction was noted in four cases (1.57%) in Cerabone and two cases (28.6%) in Cenobone group (Table 2).

Fisher's exact test showed significant differences in the frequency of foreign body reaction in samples at one month ($p<0.009$) and at two months ($p<0.028$) after biomaterial insertion. Also, according to Fisher's exact test significant differences in the frequency of foreign body reaction in the first and second months following biomaterial insertion, no significant differences in the frequency of foreign body reaction were observed in Cerabone ($p=0.59$), control($p=0.01$) or Cenobone ($p<0.1$) groups.

In terms of bone quality, most cases showed immature (woven) bone at one month (Table 3). Fisher's exact test showed no significant differences in terms of bone quality at one month after biomaterial implantation in the four groups (P=0.83). The bone was immature in most cases at two months as well. Five (71.4%), three (42.9%), four (57.1%) and three (42.9%) cases showed signs of immature bone formation in the ITB, Cerabone, control and Cenobone groups, respectively

(Table 3). According to Fisher›s exact test, no significant differences in bone quality were observed among the groups at one and two months (P=0.55).

At one and two months, no significant differences in bone quality were noted in ITB (P=0.56), Cerabone (P=0.17), control (P=0.1) and Cenobone (P=0.44) groups. At one month, three (42.9%), three (42.9%) and four (57.1%) samples in ITB, Cerabone and Cenobone groups had normal bone pattern. Only one case (3.14%) in the ITB group and one (3.14%) in Cenobone group had bone-connective tissue interface. In the remaining samples, no contact between the bone and graft was noted (Table 4).

According to Fisher's exact test, at one month following biomaterial insertion, no significant differences in terms of bone – biomaterial interface were observed (P=0.07). Two months after biomaterial insertion, greater bone-biomaterial contact was observed and four (57.1%), two (28.6%) and three (42.9%) samples in the ITB, Cerabone and Cenobone groups, respectively showed bone pattern attachment. Also, one (14.3%) sample in all three biomaterials showed connective tissue attachment and three (42.9%) in Cerabone group and one (3.14%) in Cenobone group showed bone to connective tissue attachment (Table 4).

According to Fisher›s exact test, at two months after graft placement, significant differences were found in the pattern of bone - graft attachment in the groups (P<0.02). According to Fisher's exact test, at one and two months following insertion, no significant differences were observed in ITB (P=0.1), Cerabone (P=0.16) and Cenobone (P=0.1) groups.

Discussion

The mean amount of regenerated bone in rabbit calvarial defects was not significantly different in the ITB, Cerabone xenograft (Botiss) and Cenobone (Hamanandsaz Baft Kish) groups after one and two months. In other words, the amount of newly formed bone by use of these biomaterials was similar and no significant changes occurred over time.

In addition, at one month after biomaterial implantation, significant differences were noted among the groups in terms of the remaining biomaterial but this difference was not significant at two months. At one month after biomaterial insertion, the highest amount of remaining biomaterial was noted in Cenobone and Cerabone groups while the least amount was noted in ITB. Application of Cenobone and ITB stimulated bone formation similar to Cerabone standard bone xenograft. In other words, Iranian-made bone substitutes probably have the same efficacy as the foreign-made products. Since the Iranian-made bone substitutes have been recently introduced to the market, studies on their efficacy are scarce.

Sarkarat et al, in 2010 reported no significant difference in new bone formation in human bone defects after implantation of Cenobone (Hamanandsaz Baft Kish company) and OSSEO+ (American product allograft, IMTEC company). Both biomaterials had relatively the same efficacy for preservation of alveolar ridge width and height [4].

Shahoon et al, in 2010 also found no significant difference in the amount of new bone formation after implantation of human endochondral bone matrix gelatin (HECBMG) and demineralized bone matrix (manufactured by Hamanandsaz Baft Kish company) in post-extraction sockets [5].

In another study conducted in Babol Medical University, it was shown that application of Cenobone led to osteogenesis in alveolar ridge augmentation. Clinically, it resulted in alveolar ridge preservation by 2mm and 5mm. Abolfazli et al, in 2008 reported similar results for Cerabone (DFDBA) and autogenous bone graft for treatment of periodontal intraosseous two- and three-wall defects in humans. Subjects were followed for up to six months. However, they suggested using DFDBA due to donor site bone limitation [7].

In the current study, efficient formation of new bone by the use of Cerabone, ITB and Cenobone was noted. On the other, Moghareh Abed et al, in 2011 mentioned osseointegration following the use of DFDBA around implants in dogs and stated that application of Iranian and American DFDBA had no significant difference in increasing bone-implant contact and also implant stability index in guided bone regeneration [8].

Allografts are defined as tissues harvested from one person for implantation in another person of the same species. These biomaterials are prepared from cadavers and are divided into two groups of FDBA and DFDBA. Both FDBA and DFDBA, due to high inductive protein content and less antigenic activity compared to cancellous bone, are prepared from long cortical bones. Bone allografts are available in several forms such as powder, cortical chips, spongy cubes and cortical granules [9]. High application of DFDBAs is due to the osteoinductive properties of these bone substis

tutes. The process of demineralization causes exposure of graft materials to inductive proteins embedded in the bone matrix such as BMP2 and BMP7. These proteins have the ability to induce the differentiation of mesenchymal cells to osteoblasts [10].

In addition, DFDBA provides osteoconductive surfaces required for cellular adhesion. Ideal biomaterials for use in bone regeneration must have the following characteristics: Optimal surface chemical properties for cell attachment, three-dimensional porous structure for cell growth and tissue and implant integration, mechanical strength, and biocompatibility with the host tissue. Also, they must be able to create a balance between bone resorption and bone deposition [11, 12]. Also, bone substitutes should have a proper structure for revascularization and must be able to provide adequate mechanical stability [13]. In addition, the material of the bone graft should have acceptable volume for osteogenesis. Review of the literature shows that bone graft substitutes should have the ability to produce 14-44% of bone [14,15]. Since the current study reported bone formation in mm^2, it may not be suitable for comparison with the amounts reported in other studies, although the amount of bone formation was remarkable.

Use of bone substitutes eliminates the need for surgical trauma to harvest autogenous graft; it also has the same healing power as autogenous bone [16]. As mentioned earlier, we compared the efficacy of Cenobone, ITB and Cerabone for bone regeneration in rabbit calvarial defects. It has been shown that the osteoinductive property of graft materials such as CenoBone, Cerabone and ITB depends on different variables. These variables include age of donor [17], size of granules [18] and method of preparation in tissue bank [19].

Schwartz et al, in 1998 emphasized that DFDBAs should be harvested from individuals under 50 years of age and the best age for harvesting is between 1 to 29 years [17]. Hamanandsaz Baft Kish company does not disclose any information regarding the age range of donors [3].

Size of graft material is another important factor. Size of particles in Cerabone, Cenobone and ITB is smaller than 500 microns. In this regard, the results of another study showed no significant difference in regeneration ability of particles ranging in size from 250 to 500 and 850 to 1000 microns [20]. However, the reported size of the particles is 250-750 microns; this size reportedly yields the best results in osteogenesis and bone regeneration [21].

Method of biomaterial preparation is another important factor in osteoinduction [19]. According to the manufacturer of Cenobone, all phases of processn ing and production of biomaterials are based on FDA guidelines and recommendations.

The quantity of histomorphometric characteristics reported in different studies must be interpreted and compared with caution because of different methods of taking surgical biopsies in animal versus human studies. Also, a core sample of bone may be obtained vertically or horizontally in human studies, which may affect the results [22, 23].

Conclusion

In general, Cenobone And ITB Iranian-made bone substitutes showed acceptable efficacy for bone regeneration in rabbit calvarial defects compared to Cerabone. Considering the limitations of in vitro studies, the efficacy of these biomaterials must be evaluated in the clinical setting.

Table 1. Frequency of different degrees of inflammation in the groups studied in the first and second months following biomaterial insertion in rabbit calvarial defects.

Time	Group	Without inflammation	Slight	moderate	Severe	Total
At one month	ITB	0	1 (14.3%)	3 (42.9%)	3 (42.9%)	7 (100%)
	CeraBone	0	1 (14.3%)	4 (57.1%)	2 (28.6%)	7 (100%)
	Control	1 (14.3%)	4 (57.1%)	2 (28.6%)	0	7 (100%)
	CenoBone	1 (3.6%)	1 (14.3%)	4 (57.1%)	2 (28.6%)	7 (100%)
	Total		7 (25.0%)	13 (46.4%)	7 (0.25%)	28 (100%)
At two months	ITB	2 (28.6%)	4 (57.1%)	1 (14.3%)	0	7 (100%)
	CeraBone	1 (14.3%)	1 (14.3%)	4 (57.1%)	1 (14.3%)	7 (100%)
	Control	3(42.9%)	2 (28.6%)	1 (14.3%)	1 (14.3%)	7 (100%)
	CenoBone	0	6 (85.7%)	1 (14.3%)	0	7 (100%)
	Total	6 (21.4%)	13 (46.4%)	7 (25.0%)	2 (7.1%)	28 (100%)

Table 2. Distribution of foreign body reaction in the groups in the first and second months after biomaterial insertion in rabbit calvarial defects.

Time	Group	no foreign body reaction	With foreign body reaction	Total
At 1 month	ITB	1 (14.3%)	6 (85.7%)	7 (100%)
	CeraBone	5 (71.4%)	2 (28.6%)	7 (100%)
	Control	6 (85.7%)	1 (14.3%)	7 (100%)
	CenoBone	1 (14.3%)	6 (85.7%)	7 (100%)
	Total	13 (46.4%)	15 (53.6%)	28 (100%)
At 2 months	ITB	7 (100%)	0	7 (100%)
	CeraBone	3 (42.9%)	4 (57.1%)	7 (100%)
	Control	7 (100%)	0	7 (100%)
	CenoBone	5 (71.4%)	2(28.6%)	7 (100%)
	Total	22 (78.6%)	6(21.4%)	28 (100%)

Table 3. bone quality (woven/lamellar) in the groups at one and two months after placement of biomaterials in rabbit calvarial bone defects.

Time	Group	No bone formation	woven	lamellar	woven | lamellar	Total
At one month	ITB	3 (42.9%)	4 (57.1%)	0	0	7 (100%)
	CeraBone	4 (57.1%)	3 (42.9%)	0	0	7 (100%)
	Control	2 (28.6%)	4 (57.1%)	0	1 (14.3%)	7 (100%)
	CenoBone	2 (28.6%)	5 (71.4%)	0	0	7 (100%)
	Total	11 (39.3%)	16 (57.1%)	0	1 (3.6%)	28 (100%)
At two months	ITB	1 (14.3%)	5 (71.4%)	0	1 (14.3%)	7 (100%)
	CeraBone	1 (14.3%)	3 (42.9%)	0	3 (42.9%)	7 (100%)
	Control	3 (42.9%)	4 (57.1%)	0	0	7 (100%)
	CenoBone	1 (14.3%)	3 (42.9%)	1 (14.3%)	2 (28.6%)	7 (100%)
	Total	6 (21.4%)	15 (53.6%)	1 (3.6%)	6 (21.4%)	28 (100%)

Table 4. Distribution of the type of bone – graft interface in the groups at one and two months after placement of biomaterials in rabbit calvarial bone defects.

Time	Group	Without attachment	Bone attachment	Connective tissue attachment	Bone to connective tissue interface	Total
At one month	ITB	3 (42.9%)	3 (42.9%)	0	1 (14.3%)	7 (100%)
	CeraBone	4 (57.1%)	3 (42.9%)	0	0	7 (100%)
	Control	7 (100%)	0	0	0	7 (100%)
	CenoBone	2 (28.6%)	4 (57.1%)	1 (14.3%)	0	7 (100%)
	Total	16 (57.1%)	10 (35.7%)	1 (3.6%)	1 (3.6%)	28 (100%)
At two months	ITB	2 (28.6%)	4 (57.1%)	1 (14.3%)	0	7 (100%)
	CeraBone	1 (14.3%)	2 (28.6%)	1 (14.3%)	3 (42.9%)	7 (100%)
	Control	7 (100%)	0	0	0	7 (100%)
	CenoBone	2 (28.6%)	3 (42.9%)	1 (14.3%)	1 (14.3%)	7 (100%)
	Total	12 (42.9%)	9 (32.1%)	3 (10.7%)	4 (14.3%)	28 (100%)

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