The Final Report

1. Research Title: A study on the oseteanagenesis inducement and the volume stability of the β-Tricalcium Phosphate, implanted in order to maintain the shape of the tooth extraction socket.

2. Research Institute and Address: Yonsei University Dental Hospital/ 50-1 Yonsei-ro, Seodaemun-gu, Seoul (Sinchon-dong 134)

3. Names, titles, and contact information of the Test Director, Co-authors, and Test Administrator

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4. Research Purpose and Background:

Our country has become a more aging society whereby 7% of the current population are senior citizens that are over the age of 65 years old. After 2014, we will become an aged society, with more than 14% of the population older than 65 years old. In addition to this, medical expenses have radically increased due to the extension of the human life and the consequent loss of body functions due to old age, this in itself has become a real social issue. This loss of functionality is the equivalent to the loss of teeth for various reasons within the dental field. This problem has also led to a radical increase in medical expenses due to the popularization of implant treatments. For a successful implant, the osseous tissue needs to be maintained in a healthy way. In order to achieve this, preserving the tooth extraction socket through bone grafts after extracting the tooth has become a critical surgical treatment. Although it is possible to consider autogenous bone grafts, xenografts or synthetic bone grafts are widely conducted due to the drawbacks, such as

pain and bleeding in the bone extraction region, scars and extension of operation time during autogenous bone grafts. Meanwhile, the bone graft materials most commonly used at present increase the patient's treatment costs as well as dependency on expensive imported materials since most are foreign-made. For this reason, it is essential that the products of the bone material market are localized and their technology developed. Recently, the Sorbone, consisting of pure β-Tricalcium Phosphate, was developed and approved by the KFDA. This product has the feature of complete absorption of bone during the simultaneous growth and the stomas are mutually connected with a 60~70% porosity. It has been confirmed that its characteristics are superior to existing products in most areas, and this study was conducted to confirm if there was an identical effect for various bone defects in the oral cavity.

<Reference>

Beta-tricalcium phosphate/type I collagen cones with or without a barrier membrane in human extraction socket healing: clinical, histologic, histomorphometric, and immunohistochemical evaluation.

Brkovic BM, Prasad HS, Rohrer MD, Konandreas G, Agrogiannis G, Antunovic D, Sándor GK. Clin Oral Investig. 2011 Mar 3.

Clinical evaluation alveolar ridge preservation with a beta-tricalcium phosphate socket graft.

Horowitz RA, Mazor Z, Miller RJ, Krauser J, Prasad HS, Rohrer MD. Compend Contin Educ Dent. 2009 Nov-Dec; 30(9):588-90, 592, 594 passim; quiz 604, 606.

Simple preservation of a maxillary extraction socket using beta-tricalcium phosphate with type I collagen: preliminary clinical and histomorphometric observations.

Brkovic BM, Prasad HS, Konandreas G, Milan R, Antunovic D, Sándor GK, Rohrer MD. J Can Dent Assoc. 2008 Jul-Aug; 74(6):523-8.

Sinus floor augmentation through a rotated palatal flap at the time of tooth extraction.

Nemcovsky CE, Winocur E, Pupkin J, Artzi Z. Int J Periodontics Restorative Dent. 2004 Apr; 24(2):177-83.

5. Characteristics of Medical Equipment for Clinical Trials:

(1) Item Name: Dental synthetic bone graft material

(2) License (Registration) Number: No. 11-714

(3) Product Name: Sorbone (Metabiomed, Inc.)

(4) Main Component: Pure-phase β-Tricalcium Phosphate

(5) Packing Unit: 1EA

6. Subject Disease and Indication: The subjects were patients who were suitable for the selection/exclusion standard and those who possessed various bone defects in the oral cavity, including patients in need of maxillary floor lifting or bone grafts, those with jawbone cystoma or edentulous maxilla, and any patients possible for bone defect coverage due to surrounding gingiva.

7. Estimated Research Period: May 10th, 2012 ~ May 9th, 2014

Actual Research Period: August 30th, 2012 ~ November 13th, 2014

8. Research Subject

The subjects are patients from the Oral and Maxillofacial Surgery Department at the Yonsei Univeristy Dental Hospital, who require bone grafts for bone defects due to the removal of lesions in the jawbone or tooth extraction, fit for the selection/exclusion standard, and possible for bone defect coverage due to surrounding gingiva.

9. Research Method

A. Standard of subject selections, standard of exclusion and the target number of subjects

*__Standard of Selection__

Must be over 20 years of age

Patients who have a general understanding of the research process and has signed the research consent form

Patients who can accordingly manage their oral hygiene

Patients in need of posterior recovery due to the implants

Patients in need of posterior recovery and maxillary sinus floor elevation

Patients who need a bone graft after a small cyst enucleation in the oral cavity

*__Standard for Exclusion__

Alcoholic or drug addict

Patients who are pregnant

Existence of an untreated periodontal disease

Patients with a risk of endocarditis

Unmanageable diabetes

Unmanageable high blood pressure

Patients with a severe habit of odontoprisis

Patients with a chronic infections or immune disease in the oral cavity

Existence of a hemorrhagic disease

Patients in the process of having radiation or chemical treatment

Patients with a mental disease

Patients with a suppressed immune system (taking immune suppressants or HIV infected)

Other cases that maybe prohibited from dental surgery

***Target Number of Subjects**

Target number of subjects: A total of 20 cases

B. Observation items, clinical examination items and observational examination methods

A CBCT is taken immediately after surgery as well as 6 months post-surgery, after which the volume of the bone implanted into the patient is each calculated using the Simplant software and its variation is analyzed.

*Method of Clinical Research

(1) Pre-surgical Preparation: When a patient who satisfies the selection criteria voluntarily signs the clinical trial consent form and is registered into the clinical trial then the initial examinations including clinical radiological examinations are conducted.

(2) Day of the Surgery: The lesions are removed and a bone graft is performed using the Sorbone, after which a suture is executed. A Cone-Beam CT is taken directly after the surgery.

(3) Removal of Sutures: The sutures are removed after the period of 1 week, and signs of infection are examined through a visual inspection and clinical symptoms.

(4) 6 Months Post-surgery: A Cone-Beam CT should be taken when observing the progress 6 months after the bone graft surgery.

C. Method of Statistical Analysis

The 1-Sample t-Test was initially arranged to be used since it was a simple comparison of the volume variation between the CBCT taken immediately after surgery and the CBCT taken after 6 months using a three-dimensional image analysis program (Simplant Software, Materialise, Belgium) with a CT. However, since the patients missed their scheduled check-ups, changes occur during the progress observation period Thus, the following items were statistically analyzed.

1) Examination of the volume difference within the observation groups, immediately following surgery and after post-surgery progress: Paired-samples t-test

2) Examination of the absorption rates variation in accordance to the period of progress observation and degree of complication: Scatter plot, Independent t-test, one-way ANOVA and Multiple linear regression

3) Examination of the difference from the absorption rate according to the location of the lesion (maxilla and mandible): Independent t-test

4) Examination of the contrast from the absorption rate according to the location of the incision suture: Independent t-test

10. Clinical Trial Results

A. Planned Number of Research Participants: 21 people (22 cases)

B. Actual Number of Research Participants: 16 people (17 cases)

C. Research Results

Table 1) Patient Information & Experimental Data

	Age/Sex	PMH	Sites	Diagnosis	Op name	POD f/u (Months)	Imm. Vol. (㎣)	f/u Vol. (㎣)	Absorption Rate(%)	Post-op status/ Complications
Case 1	25/F		#33	Full impacted tooth	Surgical ext.	5	833.49	544.64	34.66	n-s
Case 2	59/F	OP Hx. of benign tumors of ovary	#32,33	Apical radicular cyst	Cyst enucleation	6	1156.61	817.2	29.35	n-s
Case 3	22/F		#45	Infected dentigerous cyst	Cyst enucleation	6	1412.06	914.88	35.21	POD1M Post-op infection (fistula formation with pus discharge)
Case 4	54/F	Depressive disorder	#21,22	Apical radicular cyst	Cyst enucleation	6	3089.19	2176.27	29.55	n-s
Case 5	36/F		#32,33	Osteoblastoma	Excision	6	2088.25	787.51	62.29	n-s
Case 6	36/M		#38	Dentigerous cyst	Cyst enucleation	6	1592.99	44.5	97.21	POD2wks Post-op infection (pus discharge via #37 gingival sulcus)
Case 7	52/F	Hypothyroidism	#28	Full impacted tooth	Surgical ext.	7	1672.99	26.41	98.42	POD3wks Partial wound dehiscence
Case 8	24/F		#22	Inflammatory radicular cyst	Cyst enucleation	8	1552.67	86.43	94.43	POD1M Partial wound dehiscence(buccal area)
Case 9	44/M		#48	Dentigerous cyst	Cyst enucleation	9	1799.59	20.28	98.87	POD1wk Food impaction state
Case 10	46/M	HTN	#48	Dentigerous cyst	Cyst enucleation	9	2244.44	143.67	93.6	n-s
Case 11	31/M		#12	Apical radicular cyst	Cyst enucleation	9	544.12	256.41	52.88	POD1wk Mild wound dehiscence
Case 12	25/M		#37	CNI	Extraction	10	611.16	68.25	88.83	POD1wk Mild wound dehiscence
Case 13	45/M	DM	Mx. Ant.	NPDC	Cyst enucleation	11	668.04	90.21	86.5	POD1wk Wound dehiscence(palatal mucosa)
Case 14	42/M		#48	Dentigerous cyst	Cyst enucleation	11	1835.81	1079.26	41.21	POD3wks Post-op infection (pus discharge & I&D & drain)
Case 15(Rt.)	55/F		#48	Dentigerous cyst	Cyst enucleation	12	1028.12	525.99	48.84	Hypoesthesia, lower lip, Rt.
Case 15(Lt.)	55/F		#38	Dentigerous cyst	Cyst enucleation	12	6256.96	4976.58	20.46	n-s
Case 16	25/M		#46	Periapical granuloma	Excision	15	435.64	75.92	82.57	n-s

*CNI = Chronic nonspecific inflammation, NPDC = Nasopalatine duct cyst
**POD f/u = Follow-up period after operation
Imm. Vol. = Immediate post-op volume of the grafted Sorbone
f/u Vol. = Follow-up post-op volume of the remaining of the grafted Sorbone
Absorption Rate = {(Imm. Vol. - f/u Vol.)/ Imm. Vol.} x 100

Out of the overall 21 initial participants in the research, 5 discontinued midway and 16 actually completed in full. Among these patients, Case 15 had a cyst nucleation and Sorbone grafts on both sides, which left the total number of 17 cases available for comparison. One of those who pulled out midway through failed to appear on the surgery date and another cancelled to volunteer as a clinical research subject. The other three people received Sorbone grafts after surgery but two did not participate in the follow-up. The remaining person was exempted from the final data due to not attending a CBCT immediately after surgery. The plan was to observe their progress after 6 months but only 11 cases of progress observation was actually carried out after 6 months due to a lack of cooperation from the patients. The latest follow-up CBCT was taken 1 year and 3 months after the surgery.

Therefore, the previously planned statistical analysis method was then revised to be more segmented, and the following items were statistically analyzed.

1) Examination of the volume difference in the Sorbone's CBCT was taken immediately after the surgery and the Sorbone's CBCT carried out after a certain amount of progress**; Paired-samples t-test**

2) Examination from the effect of the progress observation period and the severity of the complications on the Sorbone's absorption rate; **Scatter plot, Independent t-test, one-way ANOVA, Multiple linear regression**

3) The difference in the Sorbone's absorption rate in the maxilla and mandible; **Independent t-test**

4) The difference in the Sorbone's absorption rate according to the location of the suture; **Independent t-test**

The volume data of Sorbone using the CBCT was measured through the Simplant software (Materialise, Belgium). The grafted bone observed in each axial cross section of the CBCT was reproduced three-dimensionally, and the width of the selected cross section in the software was integrated to calculate the volume (mm^3). The value range of the Sorbone's density threshold was set at 500~3071HU and the set value of the bone density in Simplant. (Fig. 1-3)

Fig. 1) Case 4 (Mx. Ant. Lt.) Immediate Post-op & POD6M CBCT

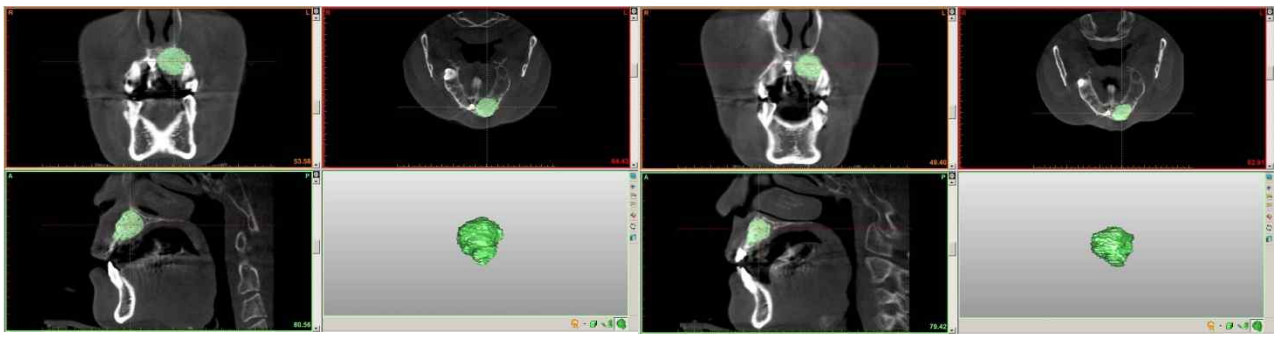


Fig. 2) Case 9 (Mn. Post. Rt.) Immediate Post-op & POD9M CBCT

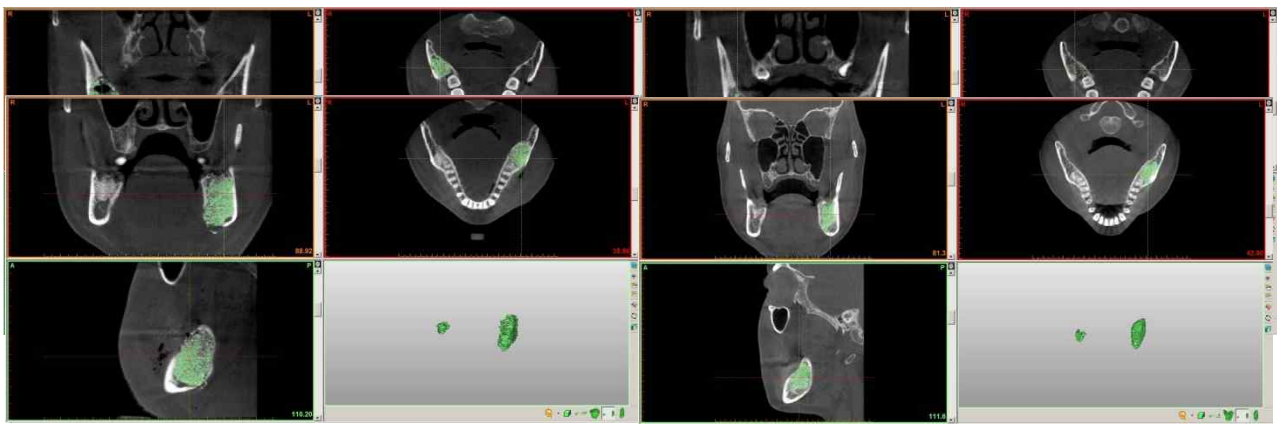


Fig. 3) Case 15 (Mn. Post. Bilateral) Immediate Post-op & POD12M CBCT

(1) Volume Variation of the Sorbone

-Paired-samples t-test

Paired Sample Statistics					
		Average	N	Standard Deviation	Standard error of the mean
Pair 1	Sorbone volume immediately after surgery	1695.4194	17	1368.63075	331.94171
	Sorbone volume after post-surgery progress observation	743.2006	17	1227.06964	297.60810

Paired sample correlation coefficient				
		N	Correlation Coefficient	P-value
Pair 1	Sorbone volume immediately after surgery & Sorbone volume after post-surgery progress observation	17	.900	.000

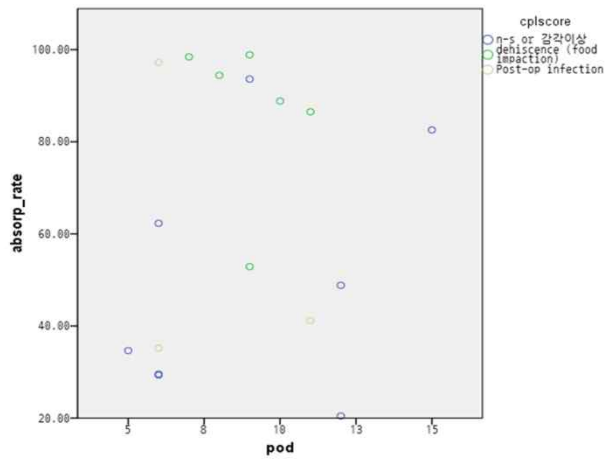
Paired Sample Examination									
		Paired difference					t	Degree of freedom	P-value (double-tail)
		Average	Standard Deviation	Standard error of mean	95% confidence interval of the difference				
					Lower limit	Upper limit			
Pair 1	Sorbone volume immediately after surgery- Sorbone volume after post-surgery progress observation	952.21882	596.85071	144.75756	645.34651	1259.09114	6.578	16	.000

; Statistically, it is shown that there is a volume difference in the Sorbone remaining immediately after surgery and after the progress observation over a certain period.

(2) Factors that affect the Sorbone's absorption rate; the progress observation period, existence and degree of complication

***Absorption Rate (%) according to POD f/u (Months)**

-Scatter plot



; Overall, it can be observed that the POD period and the absorption rate have a low correlation.

According to the degree of complication, it can be realized that the n-s (blue) group has a linear group and the dehiscence (green) group is generally highly absorbed.

***Absorption Rate (%) according to degree of complication**

-Independent t-test

Group Statistics						
	Existence of a Wound Complication		N	Average	Standard Deviation	Standard error of mean
Absorption Rate		1.00	8	50.1650	26.90324	9.51173
		2.00	9	77.0622	26.19310	8.73103

Independent Sample										
		Leven homogeneity of variance test		Average homogeneity t-test						
		F	P-value	t	Degree of Freedom	P-value (double-tail)	Mean difference	Standard error of difference	95% confidence interval of the difference	
									Lower limit	Upper limit
Absorption Rate	Assumption of equal variance	.013	.911	-2.087	15	.054	-26.89722	12.88974	-54.37105	.57661
	No assumption of equal variance			-2.083	14.083	.055	-26.89722	12.91139	-54.47300	.67856

; Difference in the absorption rate in accordance to the existence of a complication was minor while statistically insignificant.

-One-way ANOVA

Technological Statistics								
Absorption Rate(%)								
	N	Average	Standard deviation	Standard error	95% confidence interval of the difference		Minimum value	Maximum value
					Lower value	Upper value		
n-s or paresthesia	8	50.1650	26.90324	9.51173	27.6733	72.6567	20.46	93.60
Dehiscence(food impaction)	6	86.6550	17.28339	7.05591	68.5172	104.7927	52.88	98.87
Post-op infection	3	57.8767	34.19552	19.74279	-27.0697	142.8230	35.21	97.21
Total	17	64.4047	29.17532	7.07605	7.07605	79.4053	20.46	98.87

; The dehiscence group had the highest absorption rate, with a relatively consistent data (standard deviation 17.28), however, the Infection group's standard deviation was 34.20, which seems to have been affected by the number-N being too small.

One-way ANOVA					
Absorption Rate(%)					
	Sum of squares	df	Mean square	F	P-value
Between-group	4720.453	2	2360.227	3.713	**.051**
Within-group	8898.733	14	635.624		
Total	13619.186	16			

; The difference between the groups was shown to be quite minor and insignificant, even though the dehiscence group's average is much higher than the average from the other groups and the homogeneity within the group was low which led to a diluted difference.

-Multiple linear regression

Result Variables: Absorption Rate (%)

Factors: POD f/u (Months), Complication score (1; dehiscence, 2; infection)

Model Summary				
Model	R	R square	Altered R square	Standard error of estimate
1	.598[a]	.358	.210	25.93403

a. Predictive value: (constant), existence of complication score 2, POD f/u (Months), existence of complication score 1

Variance Analysis						
Model		Sum of squares	Degree of freedom	Mean square	F	P-value
1	Regression Model	4875.726	3	1625.242	2.416	.113[b]
	Residual	8743.460	13	672.574		
	Total	13619.186	16			

a. Dependent variable: Absorption Rate(%)

b. Predictive value: (constant), existence of complication score 2, POD f/u (Months), existence of complication score 1

Coefficient								
Model		Non-standardized coefficient		Standardized coefficient	t	P-value	95% confidence interval of B	
		B	Standard Error	Beta			Lower value	Upper value
1	(Constant)	40.215	22.647		1.776	.099	-8.710	89.141
	POD f/u (Months)	1.121	2.333	.108	.480	.639	-3.920	6.162
	Existence of Complication 1	36.350	14.009	.614	2.595	.022	6.085	66.614
	Existence of Complication 2	9.066	17.782	.122	.510	.619	-29.350	47.483

a. Dependent variable: Absorption Rate(%)

; Statistically, the absorption rate had increased by 1.121% during each passing month of the progress observation period. When the complication score was 1 (wound dehiscence), the absorption rate was 36.350% higher than the time when the complication score was 0 (normal healing state), and 9.066% higher when the score hits 2. Although it was statistically insignificant for POD and Complication 2, the fact that Complication score 1 crucial in statistics represents that when there is dehiscence in the operated area, the Sorbone's absorption rate escalates when there is no complication.

(3) Difference in the Sorbone's absorption rate according to the location; maxilla/ mandible

-Independent t-test

Group Statistics					
	Jaw	N	Average	Standard Deviation	Standard error of the mean
Sorbone's absorption rate	1.00	5	72.3559	29.90989	13.37611
	2.00	12	61.0914	29.53194	8.52514

Independent Sample Examination										
		Levene homogeneity of variance test		Average homogeneity t-test						
		F	P-value	t	Degree of freedom	P-value (double-tail)	Mean difference	Standard error of estimate	95% confidence interval of the difference	
									Lower limit	Upper limit
Sorbone's absorption rate	Assumption of equal variance	.042	.840	.714	15	.486	11.26453	15.77347	-22.35583	44.88489
	No assumption of equal variance			.710	7.462	.499	11.26453	15.86185	-25.77720	48.30626

; The difference in the Sorbone's absorption rate according to the bone material's location in the maxilla or mandible presents no variations since it is statistically insignificant.

(4) The difference in the Sorbone's absorption rate according to the location of the incision suture (according to whether the bone graft material is directly below the incision suture)

-Independent t-test

Group Statistics						
	Condition of the lower suture section		N	Average	Standard deviation	Standard error of the mean
Absorption rate		1.00	8	73.4308	31.46315	11.12390
		2.00	9	56.3811	26.12246	8.70749

Independent Sample Examination										
		Levene homogeneity of variance test		Average homogeneity t-test						
		F	P-value	t	Degree of freedom	P-value (double-tail)	Mean difference	Standard error of estimate	95% confidence interval of the difference	
									Lower limit	Upper limit
Sorbone's absorption rate	Assumption of equal variance	.894	.359	1.221	15	.241	17.04970	13.96443	-12.71478	46.81418
	No assumption of equal variance			1.207	13.704	.248	17.04970	14.12663	-13.31035	47.40974

; It was tested whether there was a difference in the implanted Sorbone's absorption rate when the incision suture is located directly above the bone graft material (in cases where a bone is grafted into a tooth extraction socket or in extraction parts of dentigerous cystomas or mandibular wisdom tooth) and when the incision suture is placed above the original bone, and it was shown that statistically, there was no difference in the absorption rate of the two groups.

11. Conclusion

It has been confirmed in the final progress observation using a CT that the Sorbone was grafted into the bone defect area in the oral cavity and absorbed into the body as time passed without any major complications. A new bone was formed in the grafted area. However, the newly formed bone was mainly of a low density and it seems that this has similarities to a spongy bone or a new bone with the thickness of a callus. Statistically, the correlation between the progress observation period and the Sorbone's absorption rate was detected to being extremely weak, while its correlation with local complications was also found to be quite frail. Nevertheless, the grafted Sorbone's absorption rate was significantly higher when there was a dehiscence in the operated area compared to the time when there was no complication. In addition, there was no statistical difference in the Sorbone's absorption rate depending on whether the location was maxilla or mandible, or if the location of the incision suture was directly above the bone graft material.

In conclusion, even though there is a slight difference in the level of estimation, the Sorbone tends to be absorbed without any abnormal findings and a new bone is expected to grow in the location if the Sorbone is grafted into the bone defect area within the oral cavity.