Dental alloplastic bone substitutes currently available in Korea

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Abstract (J Korean Assoc Oral Maxillofac Surg 2019;45:51-67)

As dental implant surgery and bone grafts were widely operated in Korean dentist, many bone substitutes are commercially available, currently. For commercially used in Korea, all bone substitutes are firstly evaluated by the Ministry of Health and Welfare (MOHW) for safety and efficacy of the product. After being priced, classified, and registration by the Health Insurance Review and Assessment Service (HIRA), the post-application management is obligatory for the manufacturer (or representative importer) to receive a certificate of Good Manufacturing Practice by Ministry of Food and Drug Safety. Currently, bone substitutes are broadly classified into C group (bone union and fracture fixation), T group (human tissue), L group (general and dental material) and non-insurance material group in MOHW notification No. 2018-248. Among them, bone substitutes classified as dental materials (L7) are divided as xenograft and alloplastic bone graft. The purpose of this paper is to analyze alloplastic bone substitutes of 37 products in MOHW notification No. 2018-248 and to evaluate the reference level based on the ISI Web of Knowledge, PubMed, EMBASE (1980-2019), Cochrane Database, and Google Scholar using the criteria of registered or trademarked product name.

Key words: Bone substitutes, Dental implantation, Korea

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I. Introduction

As dental implant surgery for edentulous patients became a gold standard, bone grafts such as guided bone regeneration and sinus lift were widely operated in Korean dentist. There has been increased in the number of bone substitute products available to the dental clinician. Still the autologous bone is considered to gold standard, because of its three properties with osteoconduction, osteoinduction and osteogenesis. Osteogenesis is, the property of autogenous graft, generation of new bone from osteogenic cells within the graft. Osteoinduction is the property of the autogenous graft, allogenic graft and intrinsic bone matrix proteins such as transforming growth factor and bone morphogenetic proteins (BMP) to recruit of host stem cells. Osteoconduction is the property of a mechanical structure with biocompatibility for the migration of osteogenetic cells$^{1,2}$.

Allograft has been widely used and is an attractive alternative as it avoids donor site morbidity. It has the following advantage: (1) donor site is not needed, (2) abundant supply, and (3) little risk of transmission of infectious diseases$^3$. The ideal alloplastic bone substitutes is biologically stable and maintain its volume with allowing cell infiltration and remodeling process$^4$. The alloplastic bone substitutes has various osteoconductive capabilities depending on the manufacturing methods, crystal structure, size of pores, mechanical properties, composition and absorption rate$^5$.

Hydroxyapatite (HA) is the main mineralized of bone tissue and it exerts an osteoconductive ability when grafted in the defect. Synthetic calcium phosphate ceramics ($\beta$-tricalcium...
phosphate [β-TCP] and HA) could be altered to autogenous graft, allogenic graft and xenogenic graft and it was used as block, cement, pastes, powder, granules and putty type with carboxymethyl cellulose or hyaluronic acid. In Korea, the development of implant dentistry has led to the development of many dental synthetic bone substitute in many domestic companies.

As dental implant surgery for edentulous patients became a gold standard, bone grafts such as guided bone regeneration and sinus lift were widely operated in Korean dentist. All bone substitutes used commercially in Korea are firstly evaluated by the Ministry of Health and Welfare (MOHW) for safety and efficacy of the product. They are commercialized after being priced, classified, and registration by the Health Insurance Review and Assessment Service (HIRA). The post-application management is obligatory for the manufacturer (or representative importer) to receive a certificate of Good Manufacturing Practice (GMP) by Ministry of Food and Drug Safety (MFDS).

According to Korea Food and Drug Safety (KFDS) No. 2016-156 of ‘medical device manufacturing and quality control standards’, after the approval of commercially use, the manufacturer or importer is required to renew the conformity certification every three years or immediately if the information of product changed. If any information of the product changed, the certificate of conformity should be issued or re-issued by the manufacturer or the importer. Therefore, the manufacturer or importer of registered in the MFDS could be important factors in terms of quality control of currently available bone substitutes.

However, it is difficult for clinicians to know whether the certification or the quality of product is properly managed. Therefore, the purpose of this study is to analyze ingredients, manufacturers, importers, current status and reference levels of dental synthetic bone listed in MOHW notification No. 2018-248.

II. Materials and Methods

Commercially available dental alloplastic bone substitute which was approved MOHW notification (No. 2018-248) is analyzed the details of manufacturer, importer, composition, available form, Food and Drug Administration (FDA, USA) approval.

This review of literature included studies that detailed the use of bone graft substitute in dental situation, animal, in vivo, and in vitro studies. We excluded studies in the orthopedic and neurosurgery field and those not published in English or Korean. The Google Scholar, ISI Web of Knowledge, PubMed, EMBASE (1980-2019) and Cochrane Databases were searched in February 2019 using the criteria of registered or trademarked product name. The authors read the full text of the studies and classified it according to the ‘level of evidence’ presented by Wright et al.

### III. Results

In December 2018, thirty-seven dental alloplastic substi-

### Table 1. Level of evidence for research questions

| Type                     | Level | Description                              |
|--------------------------|-------|------------------------------------------|
| Published human studies  | I     | Randomized controlled trial (RCT)        |
|                          | II    | Split-mouth study                        |
|                          | III   | Prospective cohort¹                      |
|                          |      | Systematic review with level II studies  |
|                          |      | Poor-quality RCT (e.g., <80% follow-up)  |
|                          | IV    | Case-control study²                      |
|                          |      | Retrospective cohort study²              |
|                          |      | Systematic review with under level III studies |

¹Patients were compared with a control group of patients treated at the same time and same institution.

²Patients with a particular outcome (‘cases’) were compared with those who did not have the outcome (‘controls’).

³The study was initiated after treatment was performed.
Dental alloplastic bone substitutes currently available in Korea

were two products (BIO-C [Cowellmedi, Busan, Korea] and OssPol-Dental [Genewel, Seongnam, Korea]) that were not commercially available and one product of DualPor COLLAGEN D-INJECTION (OssGen, Daegu, Korea) that was discontinued in the market. Of the remaining 34 alloplastic substitutes, 28 products (82.4%) could be obtained information and included in this review. To approve certificate of GMP from MOHW and MFDS, the company should submit the researches for safety and efficacy of its product, as same procedure as U.S. FDA. (Table 2) The researches, however, were not published and the authors could not include in this review. The available information regarding the delivery form, component, indications, morphology (porosity, biomechanical structure, particle size), and property are shown in Tables 3 to 8.

1. The products approved in FDA

Seven products were approved in FDA11-17. (Table 2) Although TCP Dental (Kasios SAS, L’Union, France) was not licensed for dental indication in intended use of FDA17. However, the authors included TCP Dental in this category because manufacturer did not distinguish between KASIOS TCP and (KASIOS) TCP Dental.

2. Registered in MOHW and commercially available information for product name, manufacturer, importer, and component

The details of dental alloplastic bone substitute which was approved by MOHW notification No. 2018-248 were analyzed. (Table 3) Among them, BIO-C and OssPol-dental were officially discontinued. CollaOss (SK Bioland, Cheonan,

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**Table 2. Dental bone graft substitutes which Food and Drug Administration (FDA) 510(k) approved**

| Product name      | Approved date (mo/day/yr) | Indications with FDA 510(k) approved                                                                 |
|-------------------|---------------------------|--------------------------------------------------------------------------------------------------------|
| Cerasorb M granules | 7/22/2005                 | Alveolar augmentation                                                                                |
|                   |                           | Filling of defects after resection, apicoectomy, and cystectomy                                       |
|                   |                           | Elevation of extraction sockets                                                                      |
|                   |                           | Elevation of the maxillary sinus floor                                                               |
|                   |                           | Filling of periodontal/perio-implant defects for GTR and GBR                                         |
| MBCP              | 12/11/2003                | Bone void filler for bony voids or gaps of the skeletal system                                       |
|                   |                           | Used with autograft as a bone graft extender                                                         |
|                   |                           | Osseous defects and/or from traumatic injury to the bone.                                            |
|                   |                           | Without initial mechanical properties. Therefore, rigid fixation techniques may often be recommended.|
|                   |                           | Gradually resorbs and is replaced with bone.                                                        |
| MBCP Plus, MBCP+  | 7/30/2007                 | Periodontal/infrabony defects                                                                       |
|                   |                           | Ridge augmentation                                                                                    |
|                   |                           | Extraction site (for implant)                                                                       |
| OSTEON            | 7/8/2010                  | Periodontal/infrabony defects                                                                       |
|                   |                           | Ridge augmentation                                                                                    |
|                   |                           | Extraction site (for implant)                                                                       |
|                   |                           | Sinus lifts                                                                                         |
| OSTEON II         | 12/26/2011                | Periodontal/infrabony defects                                                                       |
|                   |                           | Ridge augmentation                                                                                    |
|                   |                           | Extraction site (implant preparation/placement)                                                     |
|                   |                           | Sinus lifts                                                                                         |
| OSTEON III        | 9/14/2016                 | Periodontal/infrabony defects                                                                       |
|                   |                           | Ridge augmentation                                                                                    |
|                   |                           | Extraction site (implant preparation/placement)                                                     |
|                   |                           | Sinus lifts                                                                                         |
| TCP Dental        | 11/10/2004                | Cystic cavities                                                                                     |

(GTR: guided tissue regeneration, GBR: guided bone regeneration)

Jeong-Kui Ku et al: Dental alloplastic bone substitutes currently available in Korea. J Korean Assoc Oral Maxillofac Surg 2019

53
Table 3. Dental bone graft substitutes with manufactures, importer, components and inconsistency with registered in Korean Ministry of Health and Welfare and Korean Health Insurance Review and Assessment Service

| Product name                  | Manufacturer | Nationality | Importer name | Registered components | Remarks |
|------------------------------|--------------|-------------|---------------|-----------------------|---------|
| OSSABASE-HA                   | LASAK        | Czech       | Mono Dent     | HA                    | OSSABASE-HA → OssaBase-HA |
| OVIS BONE HA                 | DENTIS       | Korea       | DENTIS        | HA                    | OVIS BONE HA → Ovis Bone HA |
| COLLASSOS (BLOCK), OSSBONE COLLAGEN | SK Bioland | Korea       | SK Bioland    | HA (90%±5%)+ collagen (10%±5%) | COLLASSOS (BLOCK), OSSBONE COLLAGEN → CollaOss (BLOCK), OssBone collagen |
| COLLASSOS (PUTTY)            | SK Bioland   | Korea       | SK Bioland    | HA (90%±5%)+ collagen (10%±5%) | Role out xenograft COLLASSOS (PUTTY) → CollaOss (PUTTY) |
| COLLASSOS (SYRINGE)          | SK Bioland   | Korea       | SK Bioland    | HA (90%±5%)+ collagen (10%±5%) | Role out xenograft COLLASSOS (SYRINGE) → CollaOss (SYRINGE) |
| DUALPOR COLLAGEN D-PUTTY     | OssGen       | Korea       | OssGen        | HA (60%)+bovine atelo collagen (0.3%)+ distilled water (39.7%) | DUALPOR COLLAGEN D-PUTTY → DualPor ColLAGEN D-Putty |
| DUALPOR COLLAGEN D-INJECTION | OssGen       | Korea       | OssGen        | HA (60%)+bovine atelo collagen (0.3%)+ distilled water (39.7%) | DUALPOR COLLAGEN D-INJECTION → DualPor ColLAGEN Injection |
| BONESIGMA TCP                | SigmaGraft   | USA         | KodentTMS     | β-TCP 100%             | BONESIGMA TCP → BoneSigma TCP |
| EXCELOS INJECT               | BioAlpha     | Korea       | BioAlpha      | β-TCP etc.             | EXCELOS INJECT → ExceLOS INJECT |
| EXCELOS (TCPGLD)             | BioAlpha     | Korea       | BioAlpha      | β-TCP 100%             | EXCELOS (TCPGLD) → ExceLOS (TCPGLD) |
| EXCELOS (TCPGMD, TCPGLD)    | BioAlpha     | Korea       | BioAlpha      | β-TCP 100%             | BioAlpha → CGbio MEGA-TCP (CGL) → Mega-TCP CG bio → MegaGen MEGA-TCP (CGM, CGL) → Mega-TCP |
| MEGA-TCP (CGL)               | CGbio        | Korea       | CGbio         | β-TCP 100%             | MEGA-TCP (CGL) → MEGA-TCP |
| Mega-TCP (CGM, CGL)          | CGbio        | Korea       | CGbio         | β-TCP 100%             | MEGA-TCP (CGM, CGL) → MEGA-TCP |
| SORBONE                      | META-BIOMED   | Korea       | META-BIOMED   | β-TCP 100%             | SORBONE → Sorbone |
| SYNCERA                      | Oscotec      | Korea       | Oscotec       | β-TCP                 | SYNCERA → Syncera |
| CERASORB                     | Curasan      | Germany     | B.ITRADING    | β-TCP                 | Cerasorb → Cerasorb M |
| BIO-C                        | Cowellmedi   | Korea       | Cowellmedi    | β-TCP+HA              | BONCELOS → Boncel-Os |
| BONCELOS                     | BioAlpha     | Korea       | BioAlpha      | β-TCP+HA              | BioAlpha → CGbio BONESIGMA BCP → BoneSigma BCP |
| BONESIGMA BCP                | SigmaGraft   | USA         | KODENT TMS    | β-TCP (40%)+HA (60%)   | CERASORB M GRANULES → Cerasorb M |
| CERASORB M GRANULES          | Curasan      | Germany     | Mono Dent     | β-TCP+HA              | HAPβ-TCP → 99% β-TCP |
Table 3. Continued

| Product name          | Manufacturer | Nationality | Importer name | Registered components                                      | Remarks                  |
|-----------------------|--------------|-------------|---------------|------------------------------------------------------------|--------------------------|
| FRABONE DENTAL        | Inobone      | Korea       | Inobone       | β-TCP (40%±5%)+HA (60%±5%)                                  | FRABONE DENTAL →          |
|                       |              |             |               |                                                            | FRABONE DENTAL INJECT →  |
|                       |              |             |               |                                                            | Hyaluronic acid addition |
| GENESIS-BCP           | DIO          | Korea       | DIO           | β-TCP (40%)+HA (60%)                                        | N/S                      |
| MBCP                  | Biometlante  | France      | Purgo Biologics| β-TCP+HA                                                   | N/S                      |
| MBCP PLUS             | Biometlante  | France      | Purgo Biologics| β-TCP+HA                                                   | MBCP PLUS →              |
|                       |              |             |               |                                                            | MBCP or/with syringe type|
| NEW BONE              | GENOSS       | Korea       | GENOSS        | β-TCP+HA                                                   | NEW BONE → Newbone        |
| OSSPOL DENTAL         | Genewel      | Korea       | Genewel       | β-TCP (40%)+HA (60%)                                       | OSSPOL DENTAL → OssPol    |
| OSTEON                | GENOSS       | Korea       | GENOSS        | HA (β-TCP)                                                | N/S                      |
| OSTEON II             | GENOSS       | Korea       | GENOSS        | β-TCP+HA                                                  | N/S                      |
| OSTEON III            | GENOSS       | Korea       | GENOSS        | β-TCP+HA                                                  | N/S                      |
| OSTEON III COLLAGEN   | GENOSS       | Korea       | GENOSS        | β-TCP+porcine collagen (95%)                               | N/S                      |
| OSTEON SINUS          | GENOSS       | Korea       | GENOSS        | HA (β-TCP)                                                | Only syringe type of      |
| OVIS BONE HA          | DENTIS       | Korea       | DENTIS        | β-TCP+HA                                                  | OSTEON I, II, and III     |
| TCP Dental            | Kasios SAS   | France      | B. IMTECH     | β-TCP (95%)+HA (5%)                                        | Ovis BONE HA →           |
|                       |              |             |               |                                                            | TCP (95%)+HA (5%)         |
|                       |              |             |               |                                                            | β-TCP (99.9%)             |
| Q-OSS+                | OSTEM IMPLANT| Korea       | OSTEM IMPLANT | β-TCP (80%±5%)+HA (20%±5%)                               | N/S                      |
| TOPGEN-S              | Toplan       | Korea       | Toplan        | β-TCP (80%±5%)+HA (20%±5%)                               | N/S                      |
| INNO CAP              | Cowellmedi   | Korea       | Cowellmedi    | Calcium phosphate (100%)                                  | INNO CAP →               |
|                       |              |             |               |                                                            | INNO-CaP                 |

(HA: hydroxyapatite, β-TCP: β-tricalcium phosphate, NA: not available, N/S: nothing special)

Jeong-Kui Ku et al: Dental alloplastic bone substitutes currently available in Korea. J Korean Assoc Oral Maxillofac Surg 2019

Korea) is registered as 60% of HA, 0.3% of bovine-derived collagen (0.3%) and 39.7% of distilled water and as block, syringe and putty types. Currently, only bock and putty type are available in the manufacturer. DualPor COLLAGEN D-PUTTY and DualPor COLLAGEN D-INJECTION is available as DualPor Collagen D-Putty and DualPor Collagen Injection, but no any information could be found.

There are seven products that do not match the manufacturer or importer registered in MOHW: (1) MBCP+ (Biometlante, Vigneux-de-Bretagne, France; sold only as MBCP and MBCP syringe type, not MBCP+), (2) Excelos Inject (BioAlpha, Seongnam, Korea; produced by CGbio, Seongnam, Korea), (3) Excelos (TCPGLD) (BioAlpha; produced by CGbio, sold exclusively by Excelos), (4) Boncel-Os (BioAlpha; produced by CGbio), (5) Mega-TCP (manufactured by CGbio; MegaGen, Seoul, Korea, sold as a single product without discrimination between CGM and CGL), (6) Cerasorb and Cerasorb M granule (sold only by Curasan, Kleinostheim, Germany: Cerasorb M, registered as importer) BI Trading currently available is not available), and (7) OSTEON Sinus (GENOSS, Suwon, Korea: sold as syringe type of OSTEON I, II, or III).(Table 3)

CollaOss is listed as a dental synthetic bone in the MOHW and HIRA data. Although it was represented as xenograft in the journal(18-21); however, it was included in this review.(Table 3)

There are three products that do not match in the component registered in MOHW: (1) Cerasorb M granules (99% β-TCP not β-TCP combined with HA; Curasan), (2) FRABONE-Inject (Inobone, Cheonan, Korea: hyaluronic acid addition with HA+β-TCP), and (3) TCP Dental (99% β-TCP not 95% β-TCP combined with 5% HA).(Table 3)

As a result, out of the 33 dental bone substitutes that are currently registered in MOHW and HIRA, 28 products could be commercially available when considering the products that are different form registered information as below: Excelos (TCPGLD) and Excelos (TCPGMD, TCPGLD) are sold exclusively by Excelos, Mega-TCP (CGL) and Mega-
TCP (CGM, CGL) are sold only by Mega-TCP, Cerasorb and Cerasorb M granules are sold by Cerasorb M, Cerasorb M is 99% β-TCP, FRABONE-Inject is sold by adding hyaluronic acid, CollaOss is sold in putty and block form without syringe type, DualPor COLLAGEN D-INJECTION is not produced, and TCP Dental (99% β-TCP).

3. Analysis of dental alloplastic bone substitutes according to constituents

The main components of dental alloplastic bone substitute are tricalcium phosphate (Ca₃(PO₄)₂, β-TCP), calcium phosphate (CaP), and hydroxyapatite (Ca₁₀(PO₄)₆(OH)₂, HA) which is crystalline form of CaP (Table 4).

1) Dental alloplastic bone substitutes consist of hydroxyapatite

HA is an inorganic material which account for 65% of bone matrix and can be classified as dense and porous, sintered ceramic and non-ceramic, and bovine, coralline and synthetic depending on the origin. Typical characteristics are as below. (1) As large as the particle size, it remains for a long time with slow absorption. (2) The higher the porosity, the easier the penetration of new bone and the quicker absorbed. (3) The larger the crystallinity, the longer the absorption period. (4) Rigid and dense block-form products have high compressive strength but are susceptible to fracture. (5) The higher the porosity, the lower the strength.

Among the dental alloplastic bone substitutes allowed for use in Korea, there were four products that consisted of HA. OssaBase-HA (LASAK, Praha, Czech) has a retrospective study of guided bone regeneration in 2018, but it was obtained human study level IV due to a poor study design. However, many other animal, in vivo, and in vitro studies for osteoconductivity have been published. No journals were found for Ovis BONE HA (DENTIS, Seoul, Korea). CollaOss consists of 90% porcine-deriven HA and 10% porcine deriven collagen. It was classified as alloplastic graft in MOHW and has two types of powder and injection and clinically available products. Injection type is a mixture of biodegradable polymers such as poloxamer and hydroxypropyl methylcellulose (HPMC) to enhance injectable property, moldability and mechanical stability prevents early collapse and inhibits undesirable macrophage activity.

Of the approved products for Korean dental alloplastic bone substitute, seven products that consist with TCP were commercialization. BoneSigma TCP (SigmaGraft, Fullerton, CA, USA) has been described as one of the in vitro studies and clinically available products but no clinical studies have been published. Excelos is registered as β-TCP etc. in MOHW and has two types of powder and injection and registered. Injection type is a mixture of biodegradable polymers such as poloxamer and hydroxypropyl methylcellulose (HPMC) to enhance injectable property, moldability and hemostasis. A clinical study comparing putty type Excelos with extraction and using as BMP carriers received a human study level IV. Excelos has animal studies for BMP carrier and in vivo study for osteoconductivity. No journals were found for Mega-TCP. Sorbone (META-BIOMED, Cheongju, Korea) was validated and received human study level II by a split-mouth study as a control of cockle-shell bone substitute in socket preservation, and used as a control material for the effect of alendronate on periodontal intra-osseous defect.

| Table 4. Commercially available dental alloplastic bone substitutes according to components |
|-----------------------------------------------|
| Commercially available dental alloplastic bone substitutes | Total |
| Hydroxyapatite (HA) | 4 |
| β-Tricalcium phosphate (β-TCP) | 8 |
| β-TCP+HA | 15 |
| Calcium phosphate (CaP: composition not confirmed) | 1 |

Jeong-Kai Ku et al: Dental alloplastic bone substitutes currently available in Korea. J Korean Assoc Oral Maxillofac Surg 2019
Dental alloplastic bone substitutes currently available in Korea

SynCera (Oscotec, Seongnam, Korea) had animal and in vivo study for osteoconductivity. Cerasorb was approved by the FDA and commercially available to Cerasorb M which reduced porosity from 80% to 65%. It was received human study level I by randomized controlled trial and systematic review that was equivalent to an autogenous graft in sinus lift. It was received human study level III in cystic lesion, periodontal defect and cleft alveolus. Also, as a result of histologically sufficient alveolar bone regeneration, human study level III was obtained in extraction socket. As human study level IV, it was used with an enamel matrix derivative in the periodontal defect, peri-implant defect after immediately implantation after extraction, every lots of animal, in vivo, and in vitro studies for osteoconduction. TCP Dental was registered as 5% of HA and 95% of β-TCP in MOHW and HIRA. However, the manufacturer (Kasios SAS) and importer (B.IMTECH, Yongin, Korea) advertised as 99% of β-TCP. Many studies and FDA 510(k) also represented as SynCera (Oscotec, Seongnam, Korea) had animal and in vivo studies for osteoconduction. BoneSigma BCP (SigmaGraft) consists with 60% of HA and 40% of β-TCP. In vivo study has been published that

### Table 5. Dental bone graft substitutes which was consisted with hydroxyapatite (HA)

| Product name     | Delivery | Component          | Indication                                                                 | Morphology                        | Property                                                                 | Level of evidence |
|------------------|----------|--------------------|-----------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------|-------------------|
| OssBase-HA       | Granule  | HA-CaP (1.65), Ca₉₀(Po₄)₀(OH)₂ | Remodeling of the alveolar ridge Treatment of periodontal defects Treatment of bone defects around dental implants Sinus lift Filling of bone defects after surgical extractions to prevent alveolar atrophy Filling of bone defects after extirpation of cysts | Macro-nano bone like structure 83% interconnected porosity Narrow size ranges of available granules Enough space for bone ingrowth over large distances | Volume maintenance Low substitution rate No risk of immunological reactions or pathogen transmission | Human study level (IV: GBR) Animal, in vivo, in vitro studies |
| Ovis BONE HA     | Granule  | 100% HA            | Periodontal bone defect Intrabony defect Extraction site Ridge augmentation Sinus lift | Well-formed macro/ micro porous Porosity | Osteoconductivity Biocompatibility Non toxicity Non inflammatory nature | NA                |
| CollaOss (Block), Ossbone Collagen | Plug     | HA 90%±5%+ collagen 10%±5% | Intrabony defect | Well-formed macro/ micro porous Porosity | Easy manipulation Easy manipulation and adhesion due to collagen Slow absorption and partial remodeling | Human study (III: extraction socket IV: peri-implant defect) Animal study |
| CollaOss (Putty) | Granule  | HA 90%±5%+ collagen 10%±5% | Intrabony defect | Well-formed macro/ micro porous Porosity | Slow absorption and partial remodeling |                             |

(CaP: calcium phosphate, GBR: guided bone regeneration, NA: data not available)

Jeong-Kai Ku et al: Dental alloplastic bone substitutes currently available in Korea. J Korean Assoc Oral Maxillofac Surg 2019
Table 6. Dental bone graft substitutes which was consisted with β-tricalcium phosphate (β-TCP)

| Product name      | Delivery   | Component | Indication                                      | Morphology                        | Property                                      | Level of evidence                      |
|-------------------|------------|-----------|------------------------------------------------|-----------------------------------|-----------------------------------------------|----------------------------------------|
| BoneSigma TCP     | Powder     | β-TCP 100%| Extraction socket                               | >95% β-TCP                       | Osteoconductive                               | In vitro study                         |
|                   |            |           | Horizontal and vertical augmentation           | Interconnected macro and micro porous structure | High resorption rate: rapid osseointegration and recovery in dental implants |                                        |
|                   |            |           | Peri-implant defects                            |                                   |                                               |                                        |
|                   |            |           | Periodontal regeneration                       |                                   |                                               |                                        |
|                   |            |           | Ridge augmentation                             |                                   |                                               |                                        |
|                   |            |           | Sinus floor elevation                          |                                   |                                               |                                        |
| Excelos Inject    | Injectable | β-TCP 100%| Sinus lift                                      | β-TCP particle (size: 45-75 µm) with hydrogel (poloxamer, hydroxypropyl methylcellulose [HPMC]) | Hemostasis and injectable by poloxamer-based hydrogel High moldability Osteoconductive High resorption rate Space maintaining for new bone formation | Human study level (IV: extraction socket³°) Animal studies (for BMP carrier), in vivo, in vitro studies |
|                   |            |           | Guided bone regeneration                       |                                   |                                               |                                        |
|                   |            |           | Socket preservation                            |                                   |                                               |                                        |
| Excelos (TCPGLD)  | Powder     | β-TCP 100%| Sinus floor elevation                           | 100% β-TCP                       | Osteoconductive                               | Animal, in vitro studies               |
|                   |            |           | Alveolar bone augmentation                     | Average 80% macro-porosity (pore size: 100-300 µm) | Faster absorption and biodegrade rate Space maintaining for new bone formation |                                        |
|                   |            |           | Extraction socket preservation                 |                                   |                                               |                                        |
| MEGA-TCP (CGL)    | Powder     | β-TCP 100%| NA                                              | Porous structure like human cancellous bone >99% interconnectivity Average 75% macro-porosity (pore size: 100-300 µm) | Osteoconductive Biocompatibility Biodegradable | NA                                     |
|                   |            |           |                                                | Average 55%-60% macro-porosity   |                                               |                                        |
| Sorbone           | Powder     | β-TCP 100%| Extraction socket                               | Macro- and micro-porosity         | Osteoinduction >70% new bone formation 99% resorption | Human study (level II, socket preservation³¹ and periodontal defect³⁵) |
|                   |            |           | Cystic cavities                                |                                   |                                               |                                        |
|                   |            |           | Periodontal defects                            |                                   |                                               |                                        |
|                   |            |           | Intrabony defects                              |                                   |                                               |                                        |
|                   |            |           | Ridge augmentation                             |                                   |                                               |                                        |
|                   |            |           | Sinus floor elevation                          |                                   |                                               |                                        |
| SynCera           | Powder     | β-TCP 100%| NA                                              | Micro-meso-macro pore (pore size 5-500 µm) about 65% porosity with full range of pore size and interconnected porosity | Optimal microenvironment for osteoblast adhesion proliferation and Subsequent bone remodeling | Human study level (I: sinus³⁶, III: cystic lesion, periodontal defect, cleft alveolus³⁷, extraction socket preservation³¹, IV: peri-implant defect³⁸, periodontal defect with enamel matrix derivative ⁴⁰) Animal, in vivo, in vitro studies |
|                   |            |           | Augmentation or reconstructive treatment of alveolar ridge |                                   |                                               |                                        |
|                   |            |           | Infrabony periodontal defects                  |                                   |                                               |                                        |
|                   |            |           | Extraction socket                              |                                   |                                               |                                        |
|                   |            |           | Sinus lift                                     |                                   |                                               |                                        |
|                   |            |           | Guided tissue regeneration                     |                                   |                                               |                                        |
| Cerasorb M        | Powder     | β-TCP 99% | Sinus graft                                     | Interconnected macro-porosity     | Osteoconductive Early resorbable and angiogenesis | Human study (III: sinus graft³⁵) Animal, in vivo, in vitro for osteoconduction |
|                   |            |           | Bone loss correction                           | >90% porosity (pore size: 0.2-0.5 mm) |                                               |                                        |
|                   |            |           | Filling alveoli                                |                                   |                                               |                                        |
|                   |            |           | Periodontology                                 | 0.15-2.0 mm                      |                                               |                                        |

(BMP: bone morphogenetic proteins, NA: data not available)
| Product name       | Delivery | Component             | Indication                                      | Morphology                                      | Property                                      | Level of evidence     |
|--------------------|----------|-----------------------|------------------------------------------------|------------------------------------------------|-----------------------------------------------|-----------------------|
| Boncel-Os         | Granule  | β-TCP (70%)+ HA (30%) | Ridge augmentation                             | High porosity                                   | High biocompatibility                          | Animal study          |
|                    |          |                       | Extraction sockets                              | Interconnected porous structure                 | Osteoconduction                              |                       |
|                    |          |                       | Periodontal defect                              |                                                 | Excellent wettability                          |                       |
|                    |          |                       | Sinus lift                                      |                                                 |                                               |                       |
|                    |          |                       | Support of alveolar regeneration                |                                                 |                                               |                       |
| BoneSigma BCP     | Granule  | β-TCP (40%)+ HA (60%) | Ridge augmentation                              | Micro- and macro-porosity                       | Osteoconductive properties                    | In vivo study         |
|                    |          |                       | Extraction sockets                              |                                                 | Long-term volume stability                    |                       |
|                    |          |                       | Cystic cavities                                 |                                                 |                                               |                       |
|                    |          |                       | Sinus floor elevation                           |                                                 |                                               |                       |
|                    |          |                       | Periodontal defects                             |                                                 |                                               |                       |
|                    |          |                       | Peri-implant defects                            |                                                 |                                               |                       |
| DualPor COLLAGEN  | Block    | β-TCP (40%)+ HA (60%)+| NA                                              | Trabecular like structure                       | Biocompatibility                              | NA                    |
| D-PUTTY            |          | bovine collagen (5.5%)|                                                 | Interconnected macro- and micro-porosity 80% of| Bioabsorbable                                  |                       |
|                    |          |                       |                                                 | porosity                                       | Easy handling and moldable                    |                       |
|                    |          |                       |                                                 |                                                 | Hemostasis and anti-adhesion effect           |                       |
|                    |          |                       |                                                 |                                                 | Biocompatibility                              |                       |
|                    |          |                       |                                                 |                                                 | Bioactive                                     |                       |
|                    |          |                       |                                                 |                                                 | Osteoconductive                               |                       |
|                    |          |                       |                                                 |                                                 | Osteoinductivity                              |                       |
|                    |          |                       |                                                 |                                                 | Structural feature                            |                       |
|                    |          |                       |                                                 |                                                 | Mechanical strength                           |                       |
| FRABONE            | Granule  | β-TCP (40%)+ HA (60%) | NA                                              | Haversian canal like structure                  | Highly biocompatible and bioresorbable due    | NA                    |
|                    |          |                       |                                                 | (international patent: PCT/KR2011/005509-USA and | to hyaluronic acid                            |                       |
|                    |          |                       |                                                 | Germany), 150-300 µm macropore                  |                                               |                       |
|                    |          |                       |                                                 | Average 8.1 µm micropore                        |                                               |                       |
|                    |          |                       |                                                 | 0.7 mm size of porous particles                 |                                               |                       |
| FRABONE-Inject     | Injection| β-TCP (40%±5%)+ HA  (60%±5%)+ | NA                                              | Haversian canal like structure                  | Highly biocompatible and bioresorbable due    | NA                    |
|                    |          | coated with hyaluronic acid |                                                 | (international patent: PCT/KR2011/005509-USA and | to hyaluronic acid                            |                       |
|                    |          |                       |                                                 | Germany), 100-300 µm macropore                  |                                               |                       |
|                    |          |                       |                                                 | Average 8.1 µm micropore                        |                                               |                       |
|                    |          |                       |                                                 | 0.7 mm size of porous particles                 |                                               |                       |
| GENESIS-BCP        | Granule  | β-TCP (40%)+ HA (60%) | NA                                              | 70% of complete interconnected porosity        | Highly mechanical strength                    | Human studies         |
|                    |          |                       |                                                 | 75% macropore (300-700 µm)                      | Highly biocompatible                          | (level II: periodontal| extension defect, level IV: horizontal augmentation) |
|                    |          |                       |                                                 | 25% micropore (<10 µm)                         |                                                | Animal, in vivo, in vitro | studies for osteoconduction |
| MBCP Plus          | Granule  | β-TCP (80%)+ HA (20%) | Sinus lift augmentation                         | 70% porosity with 35% microporosity            | Permeable                                     | Human study (level IV:| extraction socket⁵) | Animal, in vivo, in vitro for osteoconduction |
|                    |          |                       | Ridge augmentation                              | 1/3 micropores (<10 µm)                        | Resorbable                                    |                       |
|                    |          |                       | Alveolar regeneration                           | 2/3 macropores (300-600 µm)                    | Hydrophilic                                   |                       |
|                    |          |                       | Alveolar regeneration                           |                                                | Bioactive                                     |                       |
|                    |          |                       | Intra-osseous pockets                           |                                                | Osteoconductive                               |                       |
|                    |          |                       |                                                 |                                                | Regeneration                                  |                       |
|                    |          |                       |                                                 |                                                |                                                |                       |
| Product name | Delivery | Component | Indication | Morphology | Property | Level of evidence |
|--------------|----------|-----------|------------|------------|----------|------------------|
| NEW BONE     | Granule  | β-TCP (80%)+ HA (20%) | Ridge augmentation Extraction site and osteotomy Cystic cavities Sinus lift Periodontal defect Periodontal/implant defects Extraction site (implant preparation/placement) Sinus lift Cystic cavities | 80% porosity (pore size: 200-400 µm) 0.2-2.0 mm size of porous particles | Osteoconductive synthetic bone graft Highly resorbable due to 80% β-TCP Easy manipulation | Animal study |
| OSTEON       | Granule/ syringe | β-TCP (30%)+ HA (70%) | Periodontal defect Periodontal/implant defects Extraction site (implant preparation/placement) Sinus lift Cystic cavities | HA coated with β-TCP Interconnected porous structure similar to that of human cancellous bone 77% porosity (pore size: 300-500 µm) Irregular shaped particles of size Particle size (granule): 0.3-2.0 mm Particle size (sinus, syringe): 0.5-2.0 mm Particle size (lifting, syringe): 0.3-1.0 mm | Osteoconductive | Human study (level III: sinus lift) Animal, in vivo, in vitro for osteoconduction |
| OSTEON II    | Granule/ syringe | β-TCP (70%)+ HA (30%) | Periodontal/implant defects Extraction site (implant preparation/placement) Sinus lift Cystic cavities | Interconnected porous structure similar to that of human cancellous bone >70% porosity (pore size: 250 µm) Irregular shaped particles of size Particle size (granule): 0.2-2.0 mm Particle size (sinus, syringe): 0.5-2.0 mm Particle size (lifting, syringe): 0.2-1.0 mm | Highly resorbable due to higher β-TCP content Easy manipulation Excellent wettability Osteoconductive | Human study (level III: extraction socket, level IV: sinus lift, vertical ridge augmentation, ridge augmentation, periodontal defect) Animal, in vivo for osteoconduction |
| OSTEON III   | Granule/ syringe | β-TCP (40%)+ HA (60%) | Periodontal/implant defects Extraction site (implant preparation/placement) Sinus lift Cystic cavities | Interconnected macror and micro porous structure <80% porosity Particle size (granule): 0.2-2.0 mm Particle size (sinus, syringe): 0.5-2.0 mm Particle size (lifting, syringe): 0.2-1.0 mm CrP=1.59 | Biocompatible Osteoconductive | Animal study (BMP carries) |
| OSTEON III   | Cylinder | β-TCP (40%)+ HA (60%)+ type I collagen (>95% porcine tendon collagen) | Alveolar bone defect | Particle size: 0.2-1.0 mm | Easy manipulation Excellent wettability | NA |
| Ovis BONE BCP | Granule  | β-TCP (80%)+ HA (20%) | Periodontal bone defect Intrabony defect Extraction site Ridge augmentation Sinus lift Cystic cavity | 70% porosity (pore size: 20 µm) Particle size: 0.3-2.0 mm | Osteoconductive Excellent wettability Easy manipulation Biocompatibility and great bioactivity | NA |
it inhibited osteoclast formation with plate-rich fibrin. Dual-pore Collagen D-Putty was registered as 60% of HA, 0.3% of bovine-derived collagen, and 39.7% of distilled water by the MOHW and HIRA. On the other hand, the manufacturer (OsGen) advertised the product as 60% HA and 40% β-TCP in 94.5% of biphasic CaP, and with an additional 5.5% bovine collagen but there are no reports of any evaluations of the evaluating its information provided. In MOHW and MFDS, Inobone has registered its products as FRABONE DENTAL and FRABONE DENTAL INJECT, but they are commercially available as FRABONE and FRABONE-Inject. FRABONE (Inobone) consists with 60% of HA and 40% of β-TCP and it was received patent in USA, Germany, and Korea as mimic the harversian canal structure. FRABONE-Inject (Inobone) is a product of hyaluronic acid addition to FRABONE, which advertised to increase moldability and absorption rate by act as soluble granules of hyaluronic acid. However, there was no related researched were found. GENESIS-BCP (DIO, Busan, Korea) consists with 60% of HA and 40% of β-TCP. It was received human study level II by prospective controlled clinical trial which results good outcome in periodontal defect. In horizontal augmentation, it was showed successful result with NanoBone (HA and silica gel matrix; Artoss GmbH, Warnemünde, Germany) in case report and it obtained human study level IV. There were many animal, in vivo, and in vitro studies for osteoconductivity. Manufacturers have the two types of MBCP as combination of HA and β-TCP as ratio as 60:40 and 20:80, and a moldable MBCP (In’Oss) made by mixing hydrogel to MBCP. However, represented importer (Purgo Biologics, Seongnam, Korea) only has granule or syringe type of MBCP+ which consists with 20% of HA and 80% of β-TCP. MBCP and MBCP+ were received in FDA 510(k) approved. There were many clinical studies from MBCP which consists with 60% of HA and 40% of β-TCP. On the other hand, MBCP+ was published only animal studies and in vitro studies. Although not introduced as MBCP+, a combination of 20% of HA and 80% of β-TCP was as same resorption and bone growth as combination of 60% of HA and 40% of β-TCP in retrospective clinical trial for extraction socket and it could be human study level IV. Newbone (GENOSS) consists with 20% of HA and 80% of β-TCP. Although there were animal and in vivo studies for osteoconductivity, no clinical studies were found. Boncel-Os consists with 30% of HA and 70% of β-TCP. It was introduced as one of clinically available products and used as BMP carrier in animal study.

### Table 7. Continued

| Product name | Component | Delivery | Indication | Property | Morphology | Level of evidence |
|--------------|-----------|----------|------------|----------|------------|------------------|
| Q-OSS+       | β-TCP (80%)+, HA (20%) | Granule | NA         | Excellent hydrophilicity, Bioconductive, Bioresorbable, Excellent osteoconductivity, Biocompatible, Bioabsorbable, Rapid osteogenesis rate | Interconnected macro and microporous Particle size: 1.0-2.0 mm | NA |
| TOPGEN-S     | β-TCP (80%)+, HA (20%) | Granule | NA         | Excellent hydrophilicity, Osteoconductive | Interconnected macro and microporous Particle size: 1.0-2.0 mm | NA |

(NA: data not available, CaP: calcium phosphate, BMP: bone morphogenetic proteins)
Table 8. Dental bone graft substitutes which was consisted with calcium phosphate

| Product name | Delivery   | Component          | Indication                  | Morphology            | Property                                      | Level of evidence |
|--------------|------------|--------------------|----------------------------|-----------------------|-----------------------------------------------|-------------------|
| INNO-CaP     | Granule    | Calcium phosphate  | Sinus lift                 | 0.41-1.4 mm of particle size | Completely resorbed and progressively replaced by normal-structured bone | NA                |

(NA: data not available)  
Jeung-Kui Ku et al: Dental alloplastic bone substitutes currently available in Korea. J Korean Assoc Oral Maxillofac Surg 2019
and lift type. OSTEON, OSTEON II, and OSTEON III were received FDA 510(k) approval\textsuperscript{13-15}. In registration of MOHW, the composition was confirmed. OSTEON and OSTEON Sinus were separated but OSTEON Sinus is not available product to commercially use. The manufacture (GENOSS) has classified OSTEON Sinus and OSTEON Lifting according to the size of syringe. In FDA 510(k), there also received approval as same as OSTEON, OSTEON Sinus, and OSTEON Lifting\textsuperscript{13}. OSTEON consists with 70% of HA and 30% of β-TCP. In retrospective clinical study for sinus lift, OSTEON alone could result well-developed lamellar bone as same as Xenograft (Bio-Oss; Osteohealth, Shirley, NY, USA) and it could be received human study level III\textsuperscript{99}. There were many animal and \textit{in vivo} studies for osteoconductivity\textsuperscript{95-98}. OSTEON II consists with 30% of HA and 70% of β-TCP. In retrospective clinical study for extraction socket, OSTEON II and OSTEON II Collagen were significantly more effective than collagen or native defect and the histological result was shown in animal studies\textsuperscript{95}. Therefore, it could be received human study level III in extraction socket. It was received human study level IV by retrospective study as control group for sinus lift\textsuperscript{100}, 6 months after vertical augmentation which particulated OSTEON II was showed no significantly difference on volume change and peri-implant marginal bone loss compared with autogenous block and allogenous block bone\textsuperscript{101}, successful results on clinical and histologically in ridge augmentation\textsuperscript{102,103}, successful outcome on graft after implant removal\textsuperscript{104}, and clinically effective on periodontal defect\textsuperscript{105}. Many animal and \textit{in vivo} studies for osteoconductivity\textsuperscript{95,97,106,107}. OSTEON III consists with 60% of HA and 40% of β-TCP. There was animal study as BMP carrier\textsuperscript{108}. Although there was no OSTEON III Collagen related study, OSTEON II Collagen had animal and \textit{in vivo} studies for osteoconductivity\textsuperscript{109,110}. Ovis BONE BCP (DENTIS) consists with 20% of HA and 80% of β-TCP. No journals were found for Ovis BONE BCP. Q-Oss+ (OSSTEM IMPLANT, Seoul, Korea) consists with 20% of HA and 80% of β-TCP. It was received human study level IV by the clinical study on peri-implant defect\textsuperscript{111}. There were \textit{in vivo} study for osteoconductivity\textsuperscript{112}.

4) Dental alloplastic bone substitutes consist with CaP (composition not confirmed)

INNO-CaP (Cowellmedi) was advertised that consists CaP, however, the composition was not clearly known and no relevant research were found.

IV. Discussion

Commercially available dental alloplastic bone substitute which was approved MOHW notification No. 2018-248 were broadly divided into 4 groups as C group (bone union and fixation group), L group (general materials), T group (human tissue), and non-insurance group. In the subcategory, there were C0 group (bone substitutes: xenograft, alloplastic graft), L7 group (dental material: dental xenograft, dental alloplastic graft), TB group (bone, demineralized bone matrix, bone block, bone chip, bone powder), non-insurance group (treatment material, human-derived bone, bone substitute containing bone morphogenetic protein \([\text{rhBMP-2}]\))\textsuperscript{11}. Among them, dental alloplastic bone substitutes in L7 of L group were included in this study.

The post-application management is obligatory for the manufacturer (or representative importer) to receive a certification of GMP by MFDS. According to FKDS No. 2016-156 of ‘medical device manufacturing and quality control standards’, the certification of GMP of human tissue or functional replacement product should be renewed every three years in article 9. According to article 10 of KFDS No. 2016-156, the certification of GMP should be reissued when any information for the products changed (change of the name of the importer or manufacturer, change of location of the importer or manufacturer). In article 12 and 15, the quality
control examination agency reports periodic on the compatibility of medical device to director of KFDA. Therefore, the manufacturer or importer of registered in the MFDS could be important factors in terms of quality control of currently available bone substitutes.

However, nineteen products (51.4%) were different information among the 37 products registered in MOHW. Four products (10.8%) were different registered ingredients from journal or advertisement including DualPor COLLAGEN D-PUTTY (OssGen), Cerasorb M granules, FRABONE-Inject, and TCP Dental. Nine products (24.3%) were differ in product name or not available including CollaOss (Syringe), Mega-TCP (CGL), Cerasorb, Cerasorb M granules, BIO-C, Excelos (TCPGMD, TCPGLD), MBCP Plus (Biometlante), OssPol DENTAL, and OSTEON Sinus. Especially, CollaOss (Block) and CollaOss (Putty) were registered as dental alloplastic bone substitute in MOHW but they were introduced as xenograft in advertisement and journals. Five products (13.5%) had different manufacturer or importer including Excelos Inject (C_gbio), Excelos (TCPGLD), Excelos (TCPGMD, TCPGLD), Mega-TCP (CGM, CGL), Boncel-Os.

For a successful clinical outcome, it cannot be overemphasized that the quality of the materials or medical device should be constant and strictly controlled. Unfortunately, it is hard to identify the certification of GMP or to verify the quality in every clinical situation. Therefore, it is necessary to leave certificate to the government agency or the company which is responsible for the product. In addition the related dental institute or academy should to consider the security on quality of the product.

Implant dentistry has become a common treatment in Korea, many studies and development have been made on implant and bone graft materials. Among dental alloplastic bone substitutes which were registered in MOHW, twenty-nine (78.4%) products were domestically produced, of which three out of seven approved by FDA were made in Korea. However, there are only ten products (27.0%) have been published with clinical study, of which six are Korean products. In the view of reference, the reference level could not be as directly same as the efficiency of the product, but it could be the basis of product selection for the clinician since minimal safety and efficiency can be regarded as verified. Reference level I received Cerasorb M (β-TCP 99%) as a sinus lift. Reference level II received Sorbone (β-TCP 100%) in extraction socket and periodontal defect in vivo. Reference level III achieved that clinically confirms safety. Cerasorb M was in peri-implant and periodontal defect, CollaOss (HA 90% and collagen 10%) in extraction socket, OSTEON (β-TCP 30% and HA 70%) in sinus lift, OSTEON II (β-TCP 70% and HA 30%) in sinus lift, TCP Dental (β-TCP 99.9%) in sinus lift. Reference level IV is insufficient to verify the efficiency, could be seen as a step that clinically confirms safety. Cerasorb M was in peri-implant and periodontal defect, CollaOss was in peri-implant defect, OssaBase-HA (HA 100%) was in guided bone regeneration, Excelos (β-TCP 100%) was in extraction socket, MBCP+ (β-TCP 80% and HA 20%) was in extraction socket, GENESIS-BCP was in ridge augmentation, OSTEON II was in sinus lift, ridge augmentation, periodontal defect achieved for reference level IV. In addition, there were many animal, in vivo, and in vitro studies for osteoconductivity or role as carrier of osteoinductive growth factors or control material.

In order to obtain MOHW and MFDS approval for commercial use in Korea, a data based on research or experiments should be required, but these data could not be included in this study because they were not publicly available. Because dental bone graft surgery has been performed in various environments such as sinus lift, ridge augmentation, cystic lesion, periodontal defect, peri-implant defect, extraction socket, it could be difficult to obtain high reference level in all dental bone grafting fields. However, it is nevertheless necessary to demonstrate the clinical level of Korean dental operation and the development level of bone graft substitutes.

In conclusion, there is not enough information about the effectiveness and safety of currently available alloplastic bone substitute in dental performance. Further clinical trials including well designed RCTs are necessary to evaluation the clinical efficacy of dental alloplastic bone substitutes in Korea. It should be aware of the limited information and developed the clinical evidences and regulations for clinicians.

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**Authors’ Contributions**

J.K.K. performed study, participated in data collection and wrote the manuscript. I.H. attributed to write the manuscript.
B.K.L. and P.Y.Y. analyzed the study, J.K.L. helped in drafting the manuscript and helped in study design. All authors read and approved the final manuscript.

**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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