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Maxillary Sinus Augmentation using TGF-β and Bone Grafting in Dogs

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Abstract

Dental implants may maintain residual alveolar ridge, avoid preparation of the healthy tooth, and provide better retention, support, and chewing functions. However, in the maxillary posterior areas the size and extension of the sinus cavities often jeopardized implantation of dental implants. The mechanisms involved in sinus augmentation and osseointegration are still not fully understood. The amount of new bone regenerated may not be adequate and the time for bone healing may take years to complete; therefore, the success rate of osseointegration in augmented sinus may be lower. Two critical processes for the enhancement of bone healing are to increase the number of local osteoprogenitor cells and to accelerate the rate of bone remodeling. TGF-β may directly or indirectly regulate cells of the bone marrow and re-establish the osteoblast phenotype and enhance new bone formation. During skeletal remodeling, bone grafting materials may also be used to induce or conduct new bone formation. The purpose of this investigation was to evaluate the potential use of TGF-β and / or bone grafting materials on sinus augmentation in vivo. Two, four and six months after sinus elevation and TGF-β and bone graft implantation, dogs were sacrificed. Results were assessed using clinical, histologic, and radiograghic techniques. SEM examination was also performed to evaluate the level of osseointegration ultrastructurally. Computed tomography (CT) showed an increase in mineralization over time for all study groups. CT showed that sinuses grafted with TGF-β/OsteoGen or autogenous bone/OsteoGen exhibited greater bone density than sites grafted with OsteoGen only. Histological results of the present study indicated that TGF-β/OsteoGen, autogenous bone/OsteoGen, and OsteoGen promoted similar amount of new blood vessels and new bone in grafted maxillary sinus. It appeared that TGF-β/OsteoGen formed more new bone marrow. New bone was formed primarily around

OsteoGen. While OsteoGen was resorbed, there were still tremendous amounts of residual OsteoGen particles after 6 months of grafting. More new bone marrows were formed as graft time increased.

Key words: TGF-β, sinus augmentation, bone grafting material, osteoinduction, osteoconduction.

Introduction

Recent prevalence survey clearly showed that tooth loss increases with age. As life expectancy increases in our society, patients with edentulous conditions are commonly noticed. Many people, demanding of higher quality of life, no longer satisfy with the traditional approach of wearing removable or full dentures. Dental implants may maintain residual alveolar ridge, avoid preparation of the healthy tooth, and provide better retention, support and chewing functions[1]. The technique of guided bone regeneration has expanded the clinical usage of dental implants by promoting and augmenting alveolar bone deficiencies. Much evidence has supported the long-term success of dental implants[1-2]. However, in the maxillary posterior area, anatomical limitations due to the size and extension of the sinus cavities have often jeopardized the placement of dental implants. The posterior maxilla has previously seen reported as the least predictable area for implant survival[3]. Causes cited include: 1) inadequate bone height; 2) poor bone quality and quantity; 3) antral pneumatization; and 4) high occlusal forces. Maxillary sinus augmentation was developed to elevate the floor of the maxillary sinus in severely resorbed maxillae and to augment the cavities with new bone to enhance bony support for implants. Tatum[4-5] reported his pioneering sinus elevation by a modified Caldwell-Luc procedure and grafted onto sinus floor with autogenous rib and iliac crestal bone. Geiger (1977) successfully placed ceramic implants in perforated sinus. Boyne and James[6] grafted the sinus floor with autogenous cancellous bone and marrow from iliac crest and placed three blade implants after 10 to 12 weeks. Holms and Hagler[7] has demonstrated the potential use of porous hydroxyapatite for sinus augmentation. Thereafter, almost all bone grafting materials have been tried and applied for maxillary sinus augmentation[1-27]. These included autogenous external cancellous or onlay graft, autogenous intraoral cancellous or onlay grafts, allografts (demineralized freeze-dried bone allografts or freeze-dried bone allografts), alloplasts (porous or nonporous HA, resorbable or nonresorbable HA, Bioglass) and xenografts (Bio-Oss or Osteograft). To date, it is still unclear which type of bone grafting material promotes best healing and provides best osseointegration.

Transforming growth factor-β (TGF-β) was discovered in 1978 as substance secreted into serum free media by transformed by a murine sarcoma virus. TGF-β is a 25,000-Da dimeric molecule consisting of two polypeptides linked together by disulfide bonds. The major effects of TGF-β are in wound healing, immunoregulation, and bone remodeling, TGF-β may directly or indirectly regulate cells of

the bone marrow and re-establish the osteoblast phenotype and enhance new bone formation[28]. In addition, TGF-β inhibit osteoclast formation and bone resorption, thereby favoring bone formation over resorption[29]. The potential use of TGF-β and various bone grafting materials in sinus grafting has not been investigated. The purpose of this in vivo study was to evaluate the healing response and bone formation stimulated by TGF-β and various bone grafting materials placed in the maxillary sinus of adult Taiwanese dogs.

Material and Methods

Eleven adult Taiwanese dogs, each weighing from 8 kg to 28 kg, were used for this study. The study was guided by the Animal Research Ethics Committee at Mackay Memorial Hospital. Twelve hours prior to surgery and during surgery, dogs received 11 mg/kg body weight of ampicillin intramuscularly and were maintained for five days 250 mg ampicillin twice daily added to their diet. For all surgical procedures, all dogs were sedated with ketamine hydrochloride 10 mg/kg body weight, and Rompun 1 cc intramuscularly. Anesthesia was supplemented with local administration of 2% xylocaine containing epinephrine (1:50.000).

The sample sizes of maxillary sinuses for TGF-β mixed with OsteoGen (HA resorb, Springdale, AR), autogenous bones mixed in a 1:1 ratio with OsteoGen and OsteoGen alone are 8, 10, and 4, respectively. Each maxillary region was draped, and an oblique caudodorsal, extraoral skin incision of approximately 5 cm was made over the most ventral aspects of the maxillary sinus. Subcutaneous tissue and the masseter muscle were divided to expose the maxillary periosteum, which was incised and elevated dorsally. The lateral wall of the maxillary sinus was approached with a surgical carbide bur to draw the outline of the bony window, approximately 12 mm horizontally and 10 mm vertically. The antral membrane was then elevated gently from the sinus floor, taking care to avoid perforation. Exposure of the maxillary sinuses were carried out bilaterally, with each sinus receiving randomly either one of the test implants: 100 μg TGF-β/100 mg OsteoGen, intraoral autogenous bones mixed OsteoGen (1:1), or controls with OsteoGen. The intraoral autogenous bone was harvested from tuberosity region in each dog. The periosteum and skin flap were replaced and sutured to achieve healing.

For the evaluation of the implants of sinus augmentation, clinical, radiographic, CT scanning, scanning electron microscopic (SEM), and histologic examination were performed.

Histologic Processing of the Specimens

The animals were sacrificed 2, 4, and 6 months after sinus augmentation, under general anesthesia. The heads of the animals were fixed by vascular perfusion with 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer following a carotid artery cut down procedure. Following this initial fixation, the maxillae were block resected, and immersed in half strength Karnovsky's fixative (Karnovsky 1965), buffered to a pH of 7.4 with 0.02 m sodium cacodylate for 48 hours at 4 ℃. After completion of fixation the specimens were stained with hematoxylin and eosin for light microscopic examination. For SEM observation, the specimens were processed with the tannic acid technique of Katsumato *et al.* (1981).

The 200 μm section was used for SEM examination for evaluation of bone -implant integration. The procedure of dehydration, embedding and sawing was the same for light microscopy specimens, as was the mounting, grinding and polishing. The chosen measured area was marked with a dental diamond wheel and ground out of the preparation along with the glass slide to prevent artifacts. The specimens were placed in acetone for 2 weeks to remove resin, mounted with silver dag, DC-sputtered with 15 to 20 nm gold in an Edwards coating units (Gibco), and then examined under scanning electron microscopy.

Results

Clinical findings

All dogs tolerated whole procedures and had uneventful recoveries. Except for some swelling and ecchymosis the wounds healed well. The sutures were removed on the seventh postoperative day. However, all dogs fed quite well after maxillary sinus augmentation. During the healing period, all dogs showed no signs of infection, inflammation, or swelling. In the gross examination of each dog, the implanted material was observed in the maxillary sinus cavity and there were no signs of inflammation in the sinus cavities of the opposite side. The grafted material formed a continuum with the original sinus floor bone.

The CT scans examinations showed an increase in mineralization over time for all treatment groups (Fig 1-3). Sinuses grafted with TGF-β/OsteoGen or autogenous bone/OsteoGen exhibited greater bone density than sites grafted with OsteoGen alone.

Histologic finding

At 2 months after grafting, there were many new blood vessels and osteocytes in grafted maxillary sinus. Woven bone with many osteoblasts was observed around the graft materials (Fig 4). These histologic findings were observed in all study animals.

At 4 months, much newly formed bone was observed in grafted maxillary sinus. The woven bone decreased in comparison with that of 2 months after grafting. Newly formed bone was observed primarily around OsteoGen. Newly formed bone had a lamellar structure. Fat cells were observed in medullary cavity. It appeared that TGF-β/OsteoGen formed more new bone marrow (Fig 5). All animals showed these histologic findings.

At 6 months, newly formed continuous cortical bone was observed in grafted maxillary sinus. Most of the grafted bone and newly formed bone at the centers of the augmented areas was resorbed. The medullary cavity was filled with many fat cells (Fig 6). It appeared that TGF-β/OsteoGen formed more new bone marrow and SEM showed the OsteoGen particles imbedded in newly formed bone (Fig 7). While OsteoGen was resorbing, there were still tremendous amounts of residual OsteoGen particles after 6 months of grafting.

Discussion

The maxxillary sinus augmentation has been commonly used for the placement of osseointegrated implants in severely resorbed posterior maxillae. The present animal study evaluated the healing response and bone formation stimulated by TGF-β and various bone grafting materials placed in the maxillary

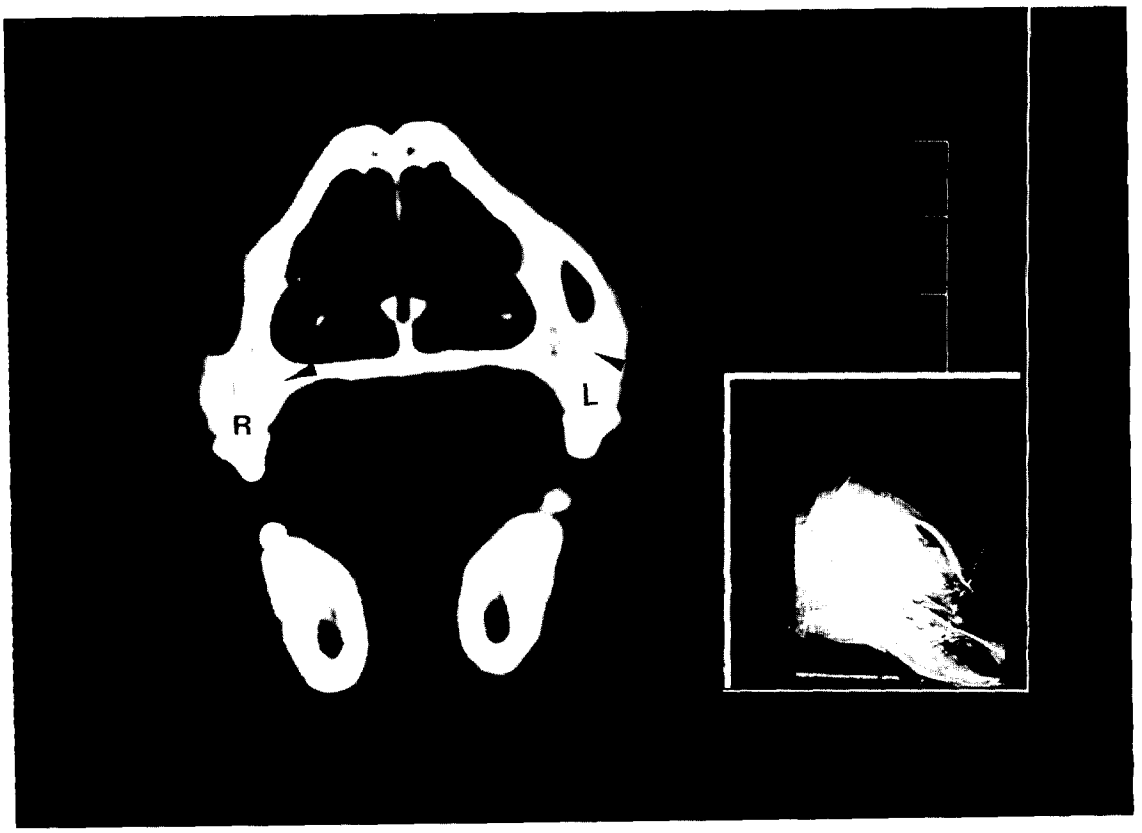

Fig 1. CT sean taken 2 months following right sinus (R) grafted with TGF-β / OsteoGen, and left sinus (L) grafted with OsteoGen alone. Sinus grafted with TGF/ β /OsteoGen exhibited greater bone density than that grafted with OsteoGen (arrow).

floor. Computed tomography (CT) showed an increase in mineralization over time for all study groups. CT showed that sinuses grafted with TGF-β OsteoGen or autogenous bone/ OsteoGen exhibited greater bone density than sites grafted with OsteoGen only. Histological results of the present study indicated that TGF-β/OsteoGen, autogenous bone/OsteoGen, and OsteoGen promoted similar amount of new blood vessels and new bone in grafted maxillary sinus. It appeared that TGF-β/OsteoGen formed more new bone marrow. New bone was formed primarily around OsteoGen. More new bone marrows were formed as graft time increased. A wide variety of specific materials have been reported in the literature for the maxillary sinus augmentation[1-10].

Kent and Block[8] demonstrated fair success rates for up to four years while simultaneously placing autogenous particulate iliac bone grafting and HA-coated implants. Intraorally harvested particulate bone has also been used to augmented subantral sinus for implant placement[9-10]. Wood and Moore[9] indicated that sinus grafting using intraoral bone has distinct advantages over extraoral iliac grafting technique. Lundgren *et al.*[10] augmented the floor with particulate mandibular symph-

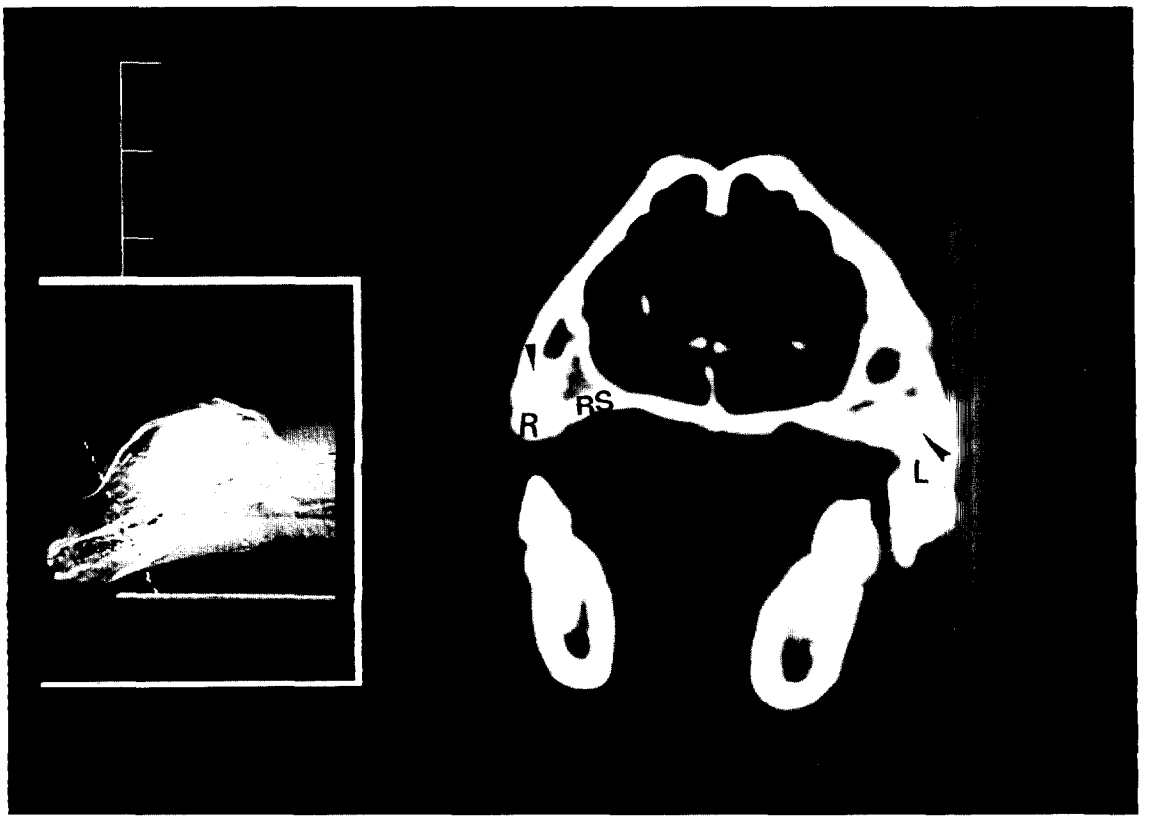

Fig 2. CT sean taken 4 months following left sinus (L) grafted with TGF-β/OsteoGen, and right sinus (R) grafted with autogenous/OsteoGen, showing increase in mineralization with time (arrow). residual maxillary sinus (RS).

ysis and placed implant fixtures six months after bone grafting. Results showed that grafting with intraoral membranous bone promoted bone volume during the 6 months healing period without loading. No implants were lost at a mean follow-up of 26 months.

Intraoral and extraoral bone blocks have been grafted on or in severely atrophic maxillae to enable insertion of endosseous implants[11-13]. Jensen & Sindet-Pedersen[11] used intramembraneous corticocancellous bone block from mandibular symphysis fixed to the residual bone by endosseous implants. 100 out of 107 implants showed normal clinical and radiographic healing for a period ranged from 6 to 32 months. Postoperative marginal resorption of the onlay grafted bone was less than 15%, which suggested that rapid resorption of iliac onlay grafts can be significantly reduced if bone from the mandibular symphysis was firmly anchored with titanium implants. Raghoebar *et al.*[12] and Triplett & Schow[13] both demonstrated that intraorally or extraorally autogenous bone block can be successfully utilized for sinus grafting to improve the potential of implant placement. The implant success in autogenous graft is more predictable if implant was placed 6 to 9 months after bone grafting. While the success rate for the grafted areas was approximately 90%, the success rate

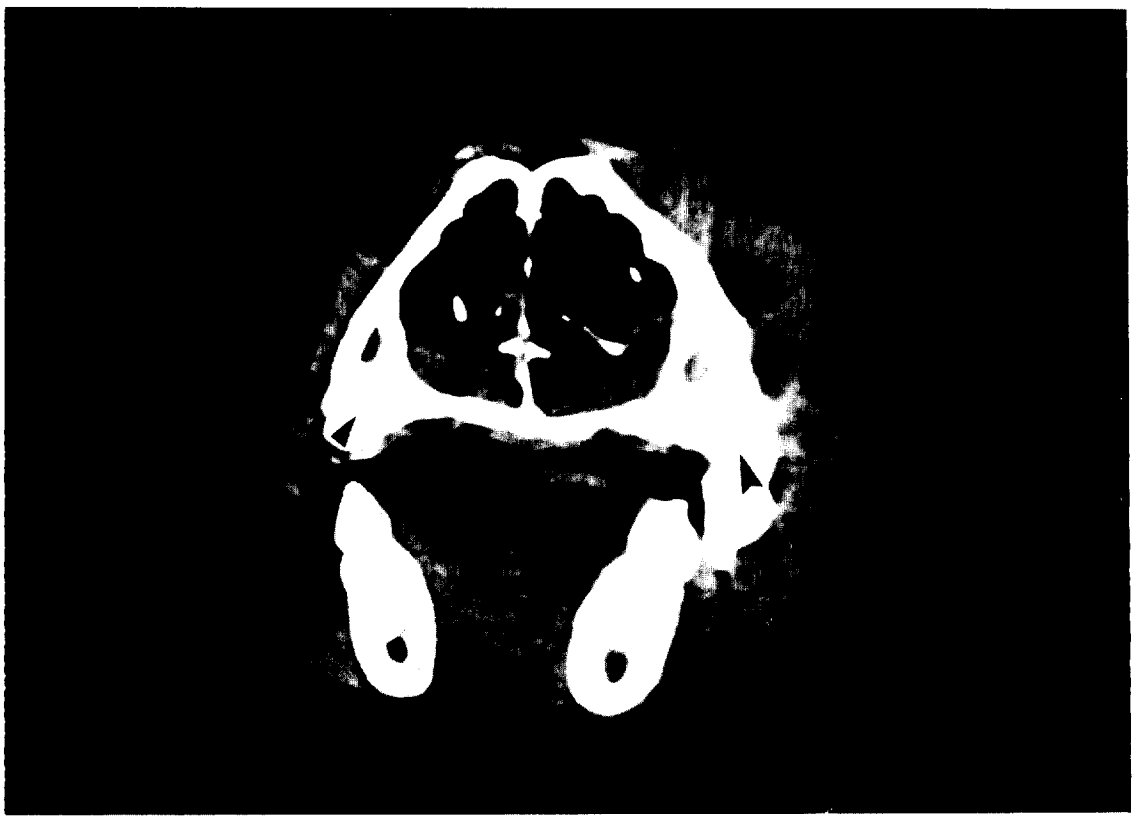

Fig 3. CT scan taken 6 months following bilateral sinuses grafted with TGF-β / OsteoGen, showing increase in mineralization as graft time increase (arrow).

for implants placed in nongrafted areas was higher than those in the grafted areas in the same group of patients.

Jesesn and Greer[14] and Nishibori *et al.*[15] compared bone healing between FDBA or DFDBA and autogenous bone grafting after sinus augmentation. Results showed that autogenous bone grafts produced bone of adequate quality and quantity for implant placement, whereas allograft alone contained remnants of the graft materials and provided inadequate ossification for the integration of implants 16 months after surgery.

Porous HA such as Interpore 200 can function as a bone graft substitute[7,16] and when combined with autogenous bone, it may enhance bone formation and osseointegration in the augmented sinus[17]. In a five-year retrospective case report, Small *et al.*[18] used a combination of DFDBA and Interpore 200 in 45 sinus grafts for 27 patients. None of the 76 restored implants have been lost. OsteoGen, resorbable, non-ceramic, non-sintered HA, or in combination with DFDBA has also been successfully used for sinus grafting, the demonstrated histologic osseointegration in a couple of case reports[19-20].

Recently, two new xenografts (Bio-Oss and Osteograf) from natural bovine bone minerals were marked and used alone[21], in combination with DFDBA[22], or with intraoral autogenous bone grafts[23] in sinus augmentation.

Fig 4. Photomicrogragh of HE-stained tissues from the dog implanted with OsteoGen. The OsteoGen particles (O) were surrounded by bone (B) and some fibrous (F) tissues. Blood vessels (V) were also observed. X 100.

Volentini & Abensu[21] showed that after implant loading for more than 2 years, the success rate ranged from 90 to 96% for 60 implants placed in 28 sinuses of 20 patients. Avera *et al.* and Wallace *et al.* found that while a significant amount of vital, mature bone was regenerated, it took up to 12 to 20 months for Bio-Oss or Osteograf to remodel to form vital bone[22-23].

Very few studies compare the relative efficacy of bone grafting materials in bone healing and osseointegration in the maxillary sinus (Moy *et al.*, 1993; Wetzel *et al.*, 1995; Huerzeler *et al.*, 1996; Wheeler *et al.*, 1996)[24-27]. Moy *et al.*[24] compared HA alone, HA plus autogenous graft, HA plus DFDBA, and autogenous graft alone in 8 sinuses of 5 patinets. The mean bone surface areas for chin bone alone, HA plus chin bone, HA alone, and HA plus DFDBA were 59.4%, 44.4%, 20.3%, 4.6% respectively.

Wetzel *et al.*[25] evaluated DFDBA, OsteoGen, and Bio-Oss in bone apposition onto implants in the sinus of a dog model. Results demonstrated that the implants surrounded by DFDBA promoted no new bone formation, whereas the sites with resorbable HA (OsteoGen) and natural cancellous bovine bone mineral (Bio-Oss) generated newly formed bone with direct contact at the implant surface.

Huerzeler *et al.*[27] determined a 5-year

Fig 5. Photomicrogragh of HE-stained tissues from the dog implanted with OsteoGen and autogenous bone. The OsteoGen particles (O) were OsteoGen and autogenous bone. The OsteoGen particles (O) were surrounded by bone (B) and abundant fibrous (F) tissues. Blood vessels (V) were observed. X 100.

clinical outcome and predictability of sinus augmentation of Bio-Oss, Interpore 200, Bi-Oss with Interpore 200 and iliac autogenous grafts, or Interpore with intraoral autogenous grafts. Result found that 90% of the placed implants were considered successful and that gender, implant length and location, remaining bone height, and type of augmentation materials used had no effect on implant success.

Wheeler *et al.*[26] compared extraoral iliac bone onlay, Bio-Oss, Interpore 200 alone or in combination with intraoral or extraoral autogenous grafts. The reasons may be due to different test materials and wide sample variations. 19 specimens were taken 4 to 36 months from the time of grafting. After six months of healing, porous HA alone produced 16.4% bone by volume, HA and hip bone 19.3%, and HA with intraoral autogenous grafts 11.3%. It took 19 to 36 months to produce greater volume of bone formation.

As regards species, human beings were used for the bone biopsy studies, whereas Taiwanese dogs were used in the present study. As regards sampling method, the bone biopsy cores revealed a limited amount of the bottom within the grafted area in the maxil-

Fig 6. Photomicrogragh of HE-stained tissues from the dog implanted with OsteoGen and TGF-β. The OsteoGen particles (O) were surrounded by bone (B) and some loose connective tissues (LCT). Blood vessels (V) were observed. X100.

lary sinus. In an experimental model, it is important that all parts of the grafted bone be evaluated.

It is difficult to extrapolate the results of this animal study to human beings. A Taiwanese dog is different from a human being with respect to maxillary sinus size and bone healing pattern. however, in human beings more further experimental studies are necessary.

Conclusion

In conclusion, these results of animal study demonstrate that maxillary sinus augmentation with TGF-β/OsteoGen or autogenous bone/OsteoGen induce comparable radiographic and histologic evidence of bone formation and that both of these treatments performed superior to the control group of OsteoGen alone based upon all methods of evaluation, however, in human beings further prospective comparative studies are necessary for full evaluation.

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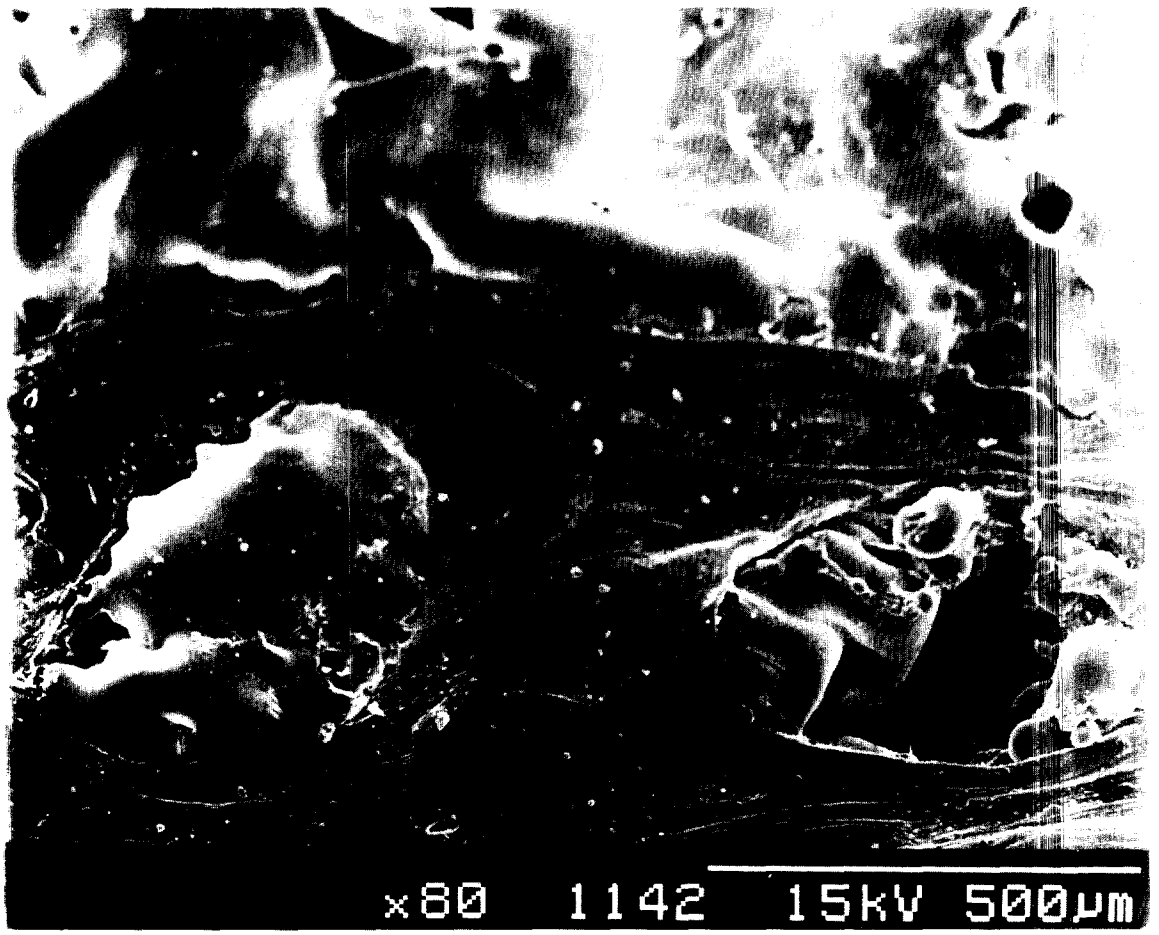

Fig 7. SEM photograph shows 6 months after sinus grafting with OsteoGen and TGF-β. The OsteoGen particles (O) were imbedded in bone (B) tissue.

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以轉化生長因子與骨移植促進上顎竇腔骨增進

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摘 要

牙科種植體已成功的被用來解決齒列缺損重建的問題，種植體可維持齒槽殘脊，可避免健康齒質之修形，提供義齒良好固位，支持及恢復咀嚼功能。然而在上顎後牙區因上顎竇及嚴重吸收之齒槽殘脊，在上顎竇底部至齒槽殘脊間，常常無法提供足夠高度和寬度之齒槽脊來種植植體。上顎竇底部增高術可增加齒槽脊之高度和寬度。許多骨移植材料被利用於上顎竇底部增高術，但是對上顎竇腔骨增進與骨整合的分子機轉乃不清楚。在骨癒合之過程中有兩個重要關鍵步驟，一為增加局部的骨先驅細胞之數目，另一為骨改造之速度。轉化生長因子可直接或間接加速骨先驅細胞之傳導或誘導，因而增進骨形成。在骨重塑階段，骨移植材料亦可用來誘導或傳導新骨形成。本研究的目的在上顎竇底部增高術時，植入轉化生長因子與骨移植材料，以期達到更理想上顎竇腔骨增進。本動物活體實驗是以十一隻臺灣土狗共二十二個上顎竇，分三組為對象。在上顎竇底部增高術時分別植入轉化生長因子混合 OsteoGen（可吸收之氫氧磷灰石），自體骨混合 OsteoGen 及單獨 OsteoGen 之對照組，其樣本數分別為 8,10,4 。並分別於術後 2,4,6 個月後犧牲，取其標本進行研究。骨增生與癒合的結果用臨床，放射線攝影，電腦斷層攝影，組織，及掃瞄電子顯微鏡評估。電腦斷層攝影結果顯示上顎竇底部植入轉化生長因子混合 OsteoGen 或自體骨混合 OsteoGen 比單獨植入 OsteoGen 之對照組的骨密度較高。組織學檢查顯示轉化生長因子混合 OsteoGen ，自體骨混合 OsteoGen 及單獨植入 OsteoGen 之對照組均有新生血管與新骨形成，各組形成新骨的量似無明顯的差異。轉化生長因子混合 OsteoGen 這組似可見較多新生骨髓。形成之新骨多位於 OsteoGen 之間， OsteoGen 雖有吸收現象，然而於移植後六個月仍可見殘餘之 OsteoGen 。移植時間較長者可見新生骨髓。本研究結果亦顯示因臺灣土狗之上顎竇大小比人類的小許多，骨癒合速度與類型也不盡相同，有待進一步施行人體研究，以期能達到實際應用於臨床病患。

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