Immediate Dental Implant Stabilization in a Canine Model Using a Novel Mineral-Organic Adhesive: 4-Month Results

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Purpose: This study evaluated a novel injectable, self-setting, osteoconductive, resorbable adhesive that provides immediate implant stabilization. Materials and Methods: Twenty-six large canines had the mandibular second through fourth premolars and the first molar removed bilaterally. After 3 months, oversized osteotomies were prepared with only the apical 2 mm of the implant engaging native bone. One site had a novel resorbable, self-setting, mineral-organic adhesive (TN-SM) placed around the implant, a second site received bone graft, and a third site received only blood clot. Removal torque, standardized radiography, and histology were used to evaluate implant stability and tissue contact after 24 hours, 10 days, and 4 months. Results: Mean removal torque values after 24 hours were 1.4, 1.3, and 22.2 Ncm for the control, bone graft, and mineral-organic adhesive, respectively. After 10 days, these values were 5.7, 6.2, and 45.7 Ncm and at 4 months increased to 88.7, 77.8, and 104.7 Ncm, respectively. Clinical, radiographic, and histologic evaluations showed a lack of inflammatory reaction. Control defects were initially radiolucent in the coronal area; grafted sites revealed particles in the gap, with both conditions gradually filling with bone over time. At 10 days, histologic evaluation demonstrated excellent biocompatibility and intimate contact of mineral-organic adhesive to both the implant and bone, providing an osseointegration-like bond; control sites revealed no bone contact in the defect area, while the bone-grafted sites revealed unattached graft particles. At 4 months, much of the mineral-organic adhesive was replaced with bone; the control and grafted sites had some bone fill, and many of the defects demonstrated no bone-to-implant contact and were filled with soft tissue or isolated graft particles. Conclusion: The mineral-organic adhesive provides immediate (osseointegration-like) and continued implant stabilization over 4 months in sites lacking primary stability. Experimental sites demonstrated maintenance of crestal bone levels adjacent to the mineral-organic adhesive and soft tissue exclusion without the use of membranes in this canine model. These results demonstrate that this novel mineral-organic adhesive can enable implant osseointegration in a site where insufficient native bone exists to allow immediate implant placement. Int J Oral Maxillofac Implants 2020;35:39–51. doi: 10.11607/jomi.7891

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Primary stability of endosseous implants in a prepared osteotomy is considered essential to successful osseointegration. Preparation of the osteotomy creates a wound in the surrounding native bone, which initiates a wound-healing inflammatory response that can lead to a lowering of implant stability, particularly in less-dense bone, followed by new bone formation and bone repair.2,3 Primary stability of an implant...
prevents excessive movement of the implant in its bony housing, which would promote a fibrous encapsulation around the implant rather than bone integration to the implant surface and a failed implant.\textsuperscript{5-7} Insertion torque is one clinical parameter that has been used as an indicator of primary implant stability. There is no broad consensus as to a minimum level of insertion torque that is acknowledged to qualify an implant as “stable” for successful osseointegration. In fact, no direct correlation has been demonstrated, nor values defined, for insertion torque that defines or predicts future implant success or failure.\textsuperscript{5,7}

Current practices in dentistry, as in medicine, emphasize minimally invasive and accelerated treatment times along with treatment protocols involving fewer procedures, all to improve the patient treatment experience without sacrificing treatment outcomes. One area in implant dentistry that continues to pose a challenge to streamlining treatment times and procedures, while maintaining consistently high success rates, is immediate placement of implants in a fresh extraction socket. The anatomy of remaining bone available for ideal positioning for prosthetic reconstruction often precludes implant primary stability. There are a number of surgical or placement alternatives to obtain adequate primary stability of the implant. Techniques such as offsetting the osteotomy to engage sound native bone, using wider-diameter implants to engage socket walls, or placing longer implants to engage bone beyond the socket apex may be feasible. However, these options frequently create restorative and/or maintenance problems posthealing due to unfavorable implant angulation or position, compromised blood supply to bony walls predisposing to bone loss, and implant exposure and limitations of relevant anatomy to longer or wider implants. If an implant cannot be appropriately placed in an immediate extraction socket, best practices call for a staged approach and ridge preservation or guided bone regeneration using various bone grafts, devices, factors, and/or membranes for implant placement after a period of time.\textsuperscript{8-11} These added procedures inherently increase the cost and healing time of treatment, and similarly increase the risk of postoperative complications, including pain, swelling, infection, and loss of graft.\textsuperscript{12,13} Most importantly, however, none of these techniques provide an opportunity to create immediate primary stability of the implant. Thus, the search continues for the technique allowing the placement of an implant in an ideal position when there is insufficient or inadequate native bone to stabilize it.

Brånemark et al defined osseointegration as bone-to-implant contact at the light microscopic level.\textsuperscript{14} When an osteotomy is prepared in native bone and an implant is placed, the implant is in contact with the cut bone surfaces, and this bone contact is called “primary bone contact.”\textsuperscript{3} Thus, the implant is osseointegrated upon placement according to this definition, and its stability is determined by this primary bone contact. At this point, however, the native bone contact begins to be remodeled, and this bone is replaced while new bone formation occurs in between the primary bone contact areas. This new bone is termed “secondary bone contact,” which ultimately determines the stability of the implant. Many years of research have shown that roughened implant surfaces are far more osteoconductive (thus enhancing secondary bone contact and faster healing times) than smoother implant surfaces, and, as such, the “dip” in stability of an implant during healing can be lessened.\textsuperscript{15,16} However, again, such enhancements in implant surface technology do not allow for stability of an implant placed in an immediate extraction site that lacks sufficient native bone to stabilize the implant or a site lacking adequate bony support for the ideal placement of an implant.

This study examines a novel mineral-organic allopastic material with adhesive properties to both bone and metal surfaces\textsuperscript{17} that enables the immediate stabilization of an implant in a site lacking enough native bone contact to stabilize the implant and allow for its placement in an ideal position. Thus, the use of this material in large immediate extraction sites, and other sites lacking native bone for primary stability of an ideally placed implant, represents a unique treatment option that has not been previously available in implant dentistry. The novel mineral-organic adhesive was used in this study to obtain primary stability of implants placed in oversized osteotomies in a canine model. This bone adhesive functions by providing immediate stabilization of the implant upon surgical placement by means of what is, in essence, an “osseointegration-like” bond. The implant is in direct contact with the adhesive, at the light microscopic level, similar to bone, providing implant stability as Brånemark defined osseointegration and Schroeder et al defined functional ankylosis.\textsuperscript{18} Further, this study aimed to assess the continued stability of implants, as well as maintenance of crestal bone levels, as the mineral-organic adhesive is replaced with bone over time.

**MATERIALS AND METHODS**

**Materials**
The mineral-organic adhesive (TN-SM) was provided by the manufacturer (Tetranite Stabilization-Material, LaunchPad Medical) in pre-dosed triturator capsules that are also used as the placement devices when used with an applicator gun. The material is composed
of calcium phosphate 61.5% w/w of solids, which is primarily composed of crystalline tetracalcium phosphate (TTCP) phase, and phosphoserine (PS) 38.5% w/w of solids, which are mixed with water. The bone graft (MC) used was a commercially available bovine bone mineral (Bio-Oss Granules 0.25 to 1.0 mm, Geistlich Pharma North America).

**Animals**
Twenty-six mixed-breed, male American hounds of at least 1 year of age, and with a body weight of more than 25 kg, were used in this study. The animals were kept in a purpose-designed room for experimental animals and fed a standard laboratory diet, with the exception of a soft food diet for the first 7 to 10 days after each surgical procedure. Prior to the experiment, the animals underwent a quarantine period to help ensure health and acclimation. The University of Texas Health Science Center at San Antonio’s Institutional Use and Care of Animals Committee approved the experimental protocol.

**Implants and Accessories**
The implants used in this study were Straumann 3.3-mm-diameter x 8-mm-length bone-level tapered sand-blasted, large-grit, acid-etched (SLA) implants (Straumann). Straumann surgical kits were used to prepare the standard-sized osteotomies. Bicon reamers (Bico) were used to oversize the coronal three-quarters of the osteotomies prior to placement of the implants.

**Study Design Summary**
This study followed a three-arm, controlled, randomized, prospective design. The mandibular second through fourth premolars and the first molar were extracted bilaterally, and tissues were allowed to heal without graft placement for at least 12 weeks. In all animals, three oversized osteotomies were prepared and implants were placed in each hemimandible. All implant sites in a given hemimandible were then used for either mechanical testing or histologic examination. At specific time points, tissues were harvested and examined as shown in Table 1. For example, four animals were enrolled in a 24-hour cohort, and all six implants in each of these animals were used for biomechanical testing only. Six animals comprised the 10-day, and five animals each the 4-month, 9-month, and 12-month cohorts, with one randomly assigned hemimandible used for biomechanical testing and the other for histologic examination. All the hemimandibles of each of the cohorts contained all three experimental conditions, which include the mineral-organic adhesive, bovine bone graft, and blood clot alone (negative control [NC]). The assignment of the mineral-organic adhesive and the bovine bone graft sites was random, as described later. All implants in the study were placed submucosally and not loaded.

**Surgical Procedures: Tooth Extraction**
Bilateral extractions of the mandibular second, third, and fourth premolars and first molar were performed under general anesthesia and aseptic conditions.

During surgery, the dogs were placed on a heating pad, administered isoflurane 4% to 5% for induction, intubated, and administered isoflurane 1.5% to 2% as inhalation anesthesia. The surgical field was disinfected with 10% povidone-iodine solution. 2% lidocaine with 1:100,000 epinephrine was administered by infiltration as a local anesthetic. Full-thickness mucoperiosteal flaps were reflected facially and lingually, and after separating the tooth roots with a rotating disk, the teeth were removed. The sharp bony edges were smoothed with a bur or hand instrument, and extraction sites were rinsed. The flaps were approximated for primary closure with nonresorbable 4-0 PTFE sutures. The sites were allowed to heal for a minimum of 12 weeks.

**Surgical Procedures: Implant Placement**
The same surgical conditions as for tooth extraction (aseptic technique and general and local anesthesia) were followed for the placement of three implants into each hemimandible. The residual ridge was prepared by exposure via full-thickness dissections and surgically planed to obtain a flat table at least 6 mm wide in the

### Table 1 Assignment of Animals and Implant Sites by Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. of animals</th>
<th>No. of TN-SM implants</th>
<th>No. of MC implants</th>
<th>No. of NC implants</th>
<th>No. of implants for biomechanical</th>
<th>No. of implants for histology</th>
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<tbody>
<tr>
<td>24-hour</td>
<td>4</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>24: 12 TN-SM, 6 NC, 6 MC</td>
<td>0</td>
</tr>
<tr>
<td>10-day</td>
<td>6</td>
<td>16</td>
<td>10</td>
<td>10</td>
<td>21: 11 TN-SM, 5 NC, 5 MC</td>
<td>15: 5 TN-SM, 5 NC, 5 MC</td>
</tr>
<tr>
<td>3-week</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>6: 6 TN-SM</td>
<td>0</td>
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<tr>
<td>4-month</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>15: 5 TN-SM, 5 NC, 5 MC</td>
<td>15: 5 TN-SM, 5 NC, 5 MC</td>
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<tr>
<td>9-month</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>15: 5 TN-SM, 5 NC, 5 MC</td>
<td>15: 5 TN-SM, 5 NC, 5 MC</td>
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<tr>
<td>12-month</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>15: 5 TN-SM, 5 NC, 5 MC</td>
<td>15: 5 TN-SM, 5 NC, 5 MC</td>
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</table>

Note that the 3-week, 9-month, and 12-month cohorts are still pending and did not contribute data to this report.

TN-SM = tetranite stabilization-material; MC = market control; NC = negative control.
buccolingual dimension in the region of implant placement, allowing for consistent placement of the platform at bone level. The middle sites were reserved for the negative control to ensure separation of the biomaterial effects, while anterior and posterior sites were randomized between the mineral-organic adhesive and bovine bone graft conditions.

Osteotomy procedure. The three standard osteotomies were prepared concurrently in each hemimandible according to the manufacturer’s instructions. Modifications to prepare the oversized osteotomies were made immediately preceding the individual implant placements. In summary, the locations of the centers of the implant osteotomies were marked with a small round bur approximately 9 mm anterior to the mesial surface of the second molar and 12 mm apart between each of the implant central axes with the aid of a Boley gauge. A second, larger round bur was used to widen the osteotomy per the implant manufacturer’s instructions, and then two spiral (Ø2.2 and 2.8 mm) tapered implant osteotomy drills were used to prepare the osteotomy to a depth of 8 mm. This process created a standard osteotomy for a 3.3-mm-diameter tapered implant at each site. Just prior to implant placement, each osteotomy was individually enlarged to 5.5-mm diameter and 6-mm depth using a sequence of five instruments (3.5, 4.2, 4.5, 5.0, and 5.5 mm in diameter) to obtain the final experimental osteotomy dimensions as displayed in Fig 1. This ensured that only the apical 2 mm of the implant engaged the bone, precluding the possibility of primary stability and presenting a worst-case scenario for the intended use of the mineral-organic adhesive. Each hemimandible in all canines received one implant representing each of the three experimental conditions: stabilization by the mineral-organic adhesive, augmentation with bovine bone graft, and a blood clot (negative control) in which no biomaterial was used, leaving the blood clot to fill the gap in the enlarged portion of the osteotomy.

Mineral-organic adhesive procedure. The adhesive was activated in a preloaded capsule provided by the manufacturer and triturated for 12 seconds. The osteotomy was filled with the material expressed from the capsule using an applicator gun once hemostasis was established and immediately prior to implant placement (Fig 2a). The implant was then placed to full depth engaging the apical bone (Fig 2b), and the excess mineral-organic adhesive was trimmed to the bony crest (Fig 2c).

Bovine bone graft procedure. At the bone graft sites, the implant was first placed to full depth, engaging the apical bone. Hydrated (sterile saline) bone graft granules were gently packed into the space surrounding the implant up to the crest of the ridge, and excess material was removed.

Blood clot (negative control) procedure. Following the standard osteotomy preparation, depth gauges were kept in place during completion of the other two sites to prevent any biomaterial from entering the negative control osteotomies. Then, the osteotomy was enlarged, the implant was placed to full depth with the cover screw already in place, and a blood clot was allowed to form in the gap as displayed in the top panel of Fig 3.

Primary closure was obtained using running 4-0 PTFE sutures. Periapical radiographs and clinical photographs (in addition to photographs taken intraoperatively) were captured immediately post-operatively and at each subsequent follow-up as shown in Fig 3.

Euthanasia

At the end of the specified in vivo period, the animals were sedated with Propofol and euthanized with an overdose of sodium pentobarbital and phenytoin (Euthasol, Virbac AH, 1 mL/10 lb) by intravenous injection.

Necropsy

The left and right hemimandibles were excised immediately following euthanasia using an oscillating autopsy saw. Hemimandibles predetermined for histologic evaluation were placed in 10% neutral buffered formalin, and hemimandibles predetermined for biomechanical testing for implant stability were placed in phosphate-buffered solution.

Biomechanical Testing: Implant Stabilization Evaluation Method

Implant stabilization was assessed through reverse torque testing. Each hemimandible was secured in a retention fixture and tested within 8 hours of harvesting. Soft tissues were removed to expose the cover screws, and torque was measured using a torque gauge (HTGS-40, Imada) while removing the cover.

![Fig 1 Osteotomy design.](image-url)
screws. If the implants did not rotate while the cover screws were removed, an implant interface adapter (Blu Sky Bio) was engaged and the reverse torque to implant removal was measured. The maximum torque value reached for each implant was recorded as the removal torque.

**Histologic Preparation**

After necropsy, the excised hemimandibles were placed in 10% neutral buffered formalin and shipped to the Hard Tissue Research Laboratory (HTRL) at the University of Minnesota (UMN) School of Dentistry for processing. The ground-section slides were stained with Stevenel's blue and Van Gieson's picro fuchsin for histologic analysis by means of bright-field and polarized light microscopic evaluation.

**Histomorphometric Analysis**

Following histologic preparation, the specimens were evaluated histomorphometrically. All the specimens were digitized at the same magnification using a Nikon Eclipse 50i microscope (Nikon Corporation) and a Spot Insight 2 mega sample digital camera (Diagnostic Instruments). Histomorphometric measurements were completed using a combination of Spot Insight program and Adobe Photoshop (Adobe Systems).

**Statistical Analysis**

Reverse torque (Ncm) mean and standard deviations are reported by cohort and treatment. Mean differences between treatment groups by cohort were tested with a linear mixed model analysis. Specifically, a model was used with both a subject-specific intercept and variances that were allowed to differ by treatment groups and cohort. Estimated differences and \( P \) values are reported. All analyses were conducted with the NCSS v11.0.2 software.

**RESULTS**

**Clinical Observations**

The oral and systemic health of all animals was monitored daily for any adverse reactions. This was accomplished by veterinarians and animal care staff, as well as study investigators. All dogs tolerated all

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**Fig 2** Injection of (a) TN-SM into osteotomy; (b) insertion of the implant; (c) trimming of the excess TN-SM.

**Fig 3** Clinical images illustrating the surgical field (top) with three experimental sites and soft tissue healing through 4 months of the postoperative period.
procedures well, recovered uneventfully from surgery, and remained healthy throughout the study. The oral condition of each animal was evaluated during the implantation phase of the study using visual inspection, radiography, and local site evaluation with the modified Gingival Index. No adverse results were noted from implantation through necropsy within the 24-hour, 10-day, and 4-month cohorts in the study. The 9-month and 12-month cohorts are currently ongoing and will be reported at a future date. No statistically significant differences were observed either between the experimental groups or the time points. Figure 3 illustrates, in a representative case, the appearance of the overlying soft tissues during the postoperative course. Note the lack of inflammatory reaction at all time points.

**Radiographic Evaluation**

The radiographic appearance of the experimental sites was evaluated for crestal bone level maintenance and changes in radiodensity adjacent to the implant. Figure 4 illustrates, in a representative case, the radiographic findings at times $t = 0$ through 4 months for a different animal than in the clinical images in Fig 3. Note the maintenance of crestal bone height and lack of radiolucency between the mineral-organic adhesive and the implant, as well as the lack of radiolucency between the mineral-organic adhesive and bone tissue, at all time points. Note the coronal radiolucency around the negative control (middle) implant and the graft particles between the implant and native bone in the coronal area of the bone-grafted site. Radiographs (and clinical images) were captured for comparative purposes between groups and for documentation of conditions.

**Implant Stabilization: Reverse Torque Testing**

Implant stability and integration were quantified by means of reverse torque testing to failure. The mineral-organic adhesive is intended to bond dental implants to bone; therefore, reverse torque application was chosen, as it directly challenges this bond by generating shear stress between the implant and bone. The biomechanical testing was performed at 24 hours, 10 days, and 4 months, with results reported in Table 2. The 9-month and 12-month cohorts are currently ongoing and will be reported at a future date.

Figure 5 illustrates the magnitude of reverse torque resistance of the implants at the experimental sites. At 24 hours in vivo, the mean of the torque required to rotate the negative control implants was 1.4 Ncm. On average, the bovine bone graft sites required 1.3 Ncm, while the mineral-organic adhesive sites required 22.2 Ncm. The mineral-organic adhesive stabilized sites demonstrated significantly higher mean reverse torque values than both the bovine bone graft sites ($P = .0191$) and the negative control sites ($P = .0197$).

After 10 days, relatively more torque is required to rotate the implant in all cases, but the reverse torque values for the mineral-organic adhesive sites remain

<table>
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<th>Table 2 Results of Reverse Torque Testing</th>
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<td>Cohort</td>
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<td>Day 1</td>
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Fig 4  Representative standardized radiographs of the experimental sites immediately post-placement and through 4 months after implant-biomaterial placement. Note the initially radiolucent central negative control site and the relatively radiodense appearance of the TN-SM (left) and the bovine bone graft (right) at the two time points.
significantly greater than either the negative control \((P = .0004)\) or the bovine bone graft \((P = .0005)\) sites. After 10 days, the mean removal torque values were 5.7, 6.2, and 45.7 Ncm for the negative control, bovine bone graft, and mineral-organic adhesive, respectively.

Following 4 months of healing, all sites continued to require more torque to rotate the implant in the bone or biomaterial. The mean 4-month reverse torque values for the negative control group, the bovine bone graft group, and the mineral-organic adhesive group were 88.7, 77.8, and 104.7 Ncm, respectively. There were no statistically significant differences between the groups; however, the mineral-organic adhesive continued to trend higher than the negative control and bovine bone graft groups.

**Histology**

Figure 6 is an overview showing each of the three experimental sites in one animal at the 10-day time point. The oversized defects are evident, as is the small amount of native bone contact in the apical portion of the preparations and the gap surrounding the implants. The drilling sequence resulted in consistent defects. Figure 6a is the mineral-organic adhesive site showing the intimate contact between the adhesive and both the implant and bone surfaces. Of additional significance is the observation that there is no soft tissue invasion along the implant, without the use of any cell occlusive membrane. Figure 6b shows the negative control that consisted of a blood clot between the osteotomy walls and the implant surface. Slight trabecular bone is present, but the majority of the implant is not integrated with any hard tissue. Figure 6c shows the results of using the particulate bovine bone graft packed around the implant. Slight new bone trabeculae are found in the apical region, but the walls of the oversized osteotomy are sharply defined, and the xenograft particles are isolated in soft tissue space without new bone formation evident.

After 4 months, more bone healing is evident in all sites as displayed in Fig 7. In Fig 7a, the mineral-organic adhesive material is well infiltrated with new bone on the buccal aspect and virtually replaced in the lingual aspect. More new bone is present in the more apical aspect of the buccal defect compared with the more coronal aspect. Note, however, that a native bony wall is maintained on the buccal aspect, extending to the top of the implant, where it narrows greatly but apparently still has good blood supply and compatibility with the mineral-organic adhesive after 4 months of contact with the material. Furthermore, new bone is evident in the most coronal area of the buccal aspect of the mineral-organic adhesive, indicating space maintenance and bone replacement of the material. On the lingual side of the implant, there is more new bone replacement of the mineral-organic adhesive. The greater new bone formation on the lingual side may be due to the implant placement being closer to the native lingual bone plate. Figure 7b (blood clot only) reveals that when the defect space is not supported, bone resorption of the native bone plates occurs, as is clearly evident on the buccal aspect. This results in the implant surface being covered with soft tissue. On the lingual aspect, maturation of the oversized osteotomy wall is evident with no bone-to-implant contact at the coronal aspect and the space filled with soft tissue. This suggests that the blood clot retracts toward the bone surface and not the implant surface, resulting in reduced bone-to-implant contact. In Fig 7c (the bovine bone-grafted site), similar findings to the negative control are evident. Isolated bone graft particles are surrounded by soft tissue on the buccal surface and, as for the negative control, significant buccal bone resorption has occurred with no bone-to-implant contact along the majority of the buccal implant surface. On the lingual aspect of this implant with xenograft, some particles are embedded in bone after 4 months, but these are far from the implant surface, and no contact with the implant surface exists. In fact, more isolated particles are present in soft tissue between the implant and this new bone. Noteworthy is the observation that even in the apical aspect of the defect on the lingual side, xenograft particles are surrounded by soft tissue and not bone. Apical to those particles is some slight new bone formation in contact with the bone surface.

Figure 8 shows a higher magnification of an implant with the mineral-organic adhesive after 10 days. The excellent biocompatibility of the adhesive to both the bone and implant is made evident by the many osteocytes present in the host bone near the mineral-organic adhesive interface. The lack of osteoclasts between the adhesive and the bone tissue is more subtle. The mineral-organic adhesive is also well adapted to the
implant surface in this 10-day specimen, indicating excellent hard material-to-implant contact, similar to the bone-to-implant contact of the osseointegrated state. Figure 9 illustrates continuing intimate contact between the remaining mineral-organic adhesive/bone complex and the implant surface after 4 months of healing. One feature to observe is the penetration of the bone through the mineral-organic adhesive to the
implant surface, resulting in excellent osseointegration. Another is the apparent transition, from the initial osseointegration-like bonding of the mineral-organic adhesive mechanically bridging the implant to bone, to the present true osseointegration of bone to titanium. Note the high degree of crestal bone height maintenance and normal macro-morphology of the newly deposited bone. Also, note the lack of apical migration of soft tissues between the implant and adhesive, as well as the lack of inflammatory infiltrate in overlying soft tissues.

**Histomorphometric Analysis**

The distance from the top of the implant apically to the first bone or biomaterial contact with the implant surface at 10 days and 4 months is shown in Fig 10. At 10 days, there was a statistical difference between the mineral-organic adhesive and negative control sites \( P < .0001 \) and the mineral-organic adhesive and bovine bone-grafted sites \( P < .0001 \). At 4 months, there was still a statistically significant difference between the mineral-organic adhesive and bovine bone-grafted sites \( P < .0071 \) with a borderline statistically significant difference between the mineral-organic adhesive and the negative control \( P = .1082 \). Indicative of maintenance of crestal hard tissue and volume preservation in the mineral-organic adhesive sites, no statistical difference appears from 10 days to 4 months in the distance of implant platform to first hard tissue contact \( P = .9828 \).

The amount of contact with bone or biomaterial after 10 days and 4 months is shown in Fig 11. At 10 days, the mineral-organic adhesive is in direct contact with 76% of the implant surface, and 4% of the surface is in contact with bone in these defects. This means that 80% of the surface is in contact with mineralized material after 10 days. At the same time point, the negative control and the bone-grafted sites have only 7% and 6% contact with hard tissue, respectively. After 4 months, the bone contact in the mineral-organic adhesive sites increases to 44% and the mineral-organic adhesive decreases to 24% (a combined mineralized material contact of 68%), indicating resorption of the mineral-organic adhesive and replacement with direct new bone deposition on the implant surface. Both the negative control (7% to 35%) and bovine bone-grafted sites (6% to 30%) had statistically significant increases in bone-to-implant contact at 4 months compared with 10 days, but neither approached the level of the mineral-organic adhesive site (44% vs 35% and 30%, respectively). In the 4-month specimens, the mineral-organic adhesive had statistically significantly more bone-to-implant contact \( P = .0335 \) than the bone-grafted sites. Furthermore, the mineral-organic adhesive also had statistically significantly less connective tissue than the bone-grafted site \( P = .0354 \) at this time point. In summary, the mineral-organic adhesive had 80% mineralized material contact at 10 days, compared with 7% and 6% for the negative control and bovine bone-grafted sites, respectively. After 4 months, the mineral-organic adhesive had 68% mineralized material contact, while the negative control and bovine bone-grafted sites had 35% and 30%, respectively.

In order to evaluate tissue composition over time, a region of interest was defined in the defect area near the coronal portion of the implant and compared at 10 days and 4 months as shown in Fig 12. All sites demonstrated a significant increase in bone content from 10 days to 4 months (mineral-organic adhesive \( P < .0001 \), negative control \( P = .0010 \), and bovine bone graft \( P = .0156 \)). With respect to soft tissue/bone marrow within the region of interest between 10 days and 4 months, there was a statistically significant difference between the mineral-organic

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**Fig 9** Photomicrograph of a TN-SM site at 4 months after implantation showing maintenance of TN-SM adhesion and replacement of adherent TN-SM by osseointegrating bone (sagittal plane, ground section, Stevenel’s blue, and Van Gieson’s picrow-fuchsin, original magnification 20X). CB = crestal bone; HB = host bone; NB = new bone.

**Fig 10** First implant contact distances. *\( P < .05 \); **\( P < .001 \).
adhesive and bovine bone graft \((P = .0002, P = .0002,\) respectively), and the mineral-organic adhesive and the negative control \((P < .0001, P = .0002,\) respectively). Very interestingly, in the mineral-organic adhesive sites, there was no difference in the total amount of soft tissue/bone marrow from 10 days to 4 months \((P = .7246).\) In summary, the mineral-organic adhesive sites demonstrated a statistically significant decrease in the amount of material present (from 64% to 34%, \(P = .0005),\) while also showing a statistically significant increase in bone content (from 3% to 39%, \(P < .0001).\) When compared with the bovine bone-grafted sites, the mineral-organic adhesive demonstrated an improvement in the amount of bone content in the region of interest at 4 months. Noteworthy, however, at 4 months, the amount of bone in the mineral-organic adhesive sites was not different than the negative control sites, indicating that while the mineral-organic adhesive fills the gap at the time of implant placement, by 4 months, it is significantly replaced by bone and does not act as a barrier to bone formation.

**DISCUSSION**

Currently, placement of implants cannot be accomplished in the correct restorative position when initial or primary stability cannot be achieved. This often occurs in large extraction sites or areas of the jaw that are missing critical bone volume or have poor bone quality. In these cases, alternative treatment approaches are required and include staged procedures with bone grafts, growth enhancers, and/or various types of barrier membranes. These approaches not only increase costs and delay implant placement, they also increase the risk of complications. Therefore, a technique to stabilize an implant when there is insufficient native bone present would be of obvious and tremendous benefit to both the patient and the dentist. Furthermore, if such a technique (1) ensures space maintenance and predictable crestal bone maintenance, (2) continuously stabilizes the implant, (3) is simultaneously replaced by bone while functioning, and (4) continues to gain strength with time, that technique would both be of significant value and likely allow implant therapy to those unable to benefit from it today.
In this study in canines, a model was created to mimic large extraction sites where implants would not be stable when placed. Three sites were created in each hemimandible where a negative control (blood clot), a bovine bone graft, and a novel mineral-organic adhesive could be examined in a controlled manner. The mineral-organic adhesive, the test material, is a strong wet-field adhesive that bonds to both bone and metal. It has been studied previously in rats, rabbits, dogs, and sheep. Unlike many of the currently used and proposed bone cements and bone regenerative materials that contain polymers, eg, acrylates and urethanes or high-density ceramics; or foreign ion-enous bone proteins, osteopontin and osteocalcin, the mineral-organic adhesive composition is not only simple but also would not be expected to present the challenge of a foreign substance to the host because of the endogenous character of the constituents. The three components of the material are calcium phosphate, primarily tetracalcium phosphate (TTCP), phosphoserine, and water. Tetracalcium phosphate has been associated with physiologic bone mineralization. Phosphoserine is not only a common metabolite, being a precursor to glycine, serine, heme, and glutathione de novo biosynthesis, but is also a major component of the noncollagenous bone proteins, osteopontin and osteocalcin, in vertebrates. Relevant properties for the use of this adhesive in this canine oral model include its adhesive characteristics to both bone and implants, self-setting nature, mild exothermy, noninflammatory characteristics, space-maintaining properties, and desirable soft tissue interaction. Additionally, the adhesive was easily and consistently injected into the extraction sockets with use of the applicator gun, following the manufacturer’s instructions for use as demonstrated in Fig 2.

A major question related to the test material was if it could provide immediate stability to an implant placed in an oversized osteotomy where the implant is not stabilized by native bone. The model utilized in this experiment consistently provided such unstable conditions as evidenced by extremely low removal torque values after 1 day (Fig 5) of healing in the negative control sites, which were located in the middle of the three sites in each hemimandible. Further evidence demonstrating the lack of native bone to stabilize the implant was found in the negative control histologic preparations (Figs 6b and Fig 7b), where the walls of the oversized osteotomy were located some distance from any native bone for the vast majority of the implant surface, particularly from the top of the implant to the very apical area where only bone marrow and cancellous bone (no cortical bone) were present. Under these conditions, the mineral-organic adhesive provided excellent implant stability (> 22 Ncm) when first measured after only 24 hours of healing. This stability was significantly greater than both the negative control and the site with bone graft particles (Table 2 and Fig 5). Thus, the first question, as to whether the test material can provide immediate stabilization of an implant not stably supported by native bone, was clearly demonstrated.

Other major questions revolved around the ability of the test material to provide continued implant stability during the healing process, if simultaneous native bone replacement of the test material would occur, whether ridge width (space) would be maintained, and if crestal bone formation occurred at the top of the implant. With respect to providing continued implant stabilization, the average removal torque value at 10 days was 210% higher than at 24 hours, and the 4-month removal torque value was 223% higher than the 10-day value. Thus, there was a steady and significant increase in implant removal torque value, indicating an increase in the strength of the bond between the implant and bone with the test material. In fact, after only 10 days, the average removal torque value was greater than the range of torque recommended for abutment placement by many implant manufacturers. Histologic analyses confirmed that the amount of native bone had significantly increased along the implant surface, demonstrating that the amount of implant osseointegration was significantly increasing over time (Fig 11). Radiographic (Fig 4) and clinical evaluations (Fig 3) confirm biocompatibility of the material with no evidence of inflammatory reaction in adjacent hard and soft tissues. Histology shows further evidence of biocompatibility of the mineral-organic adhesive with evidence of viable osteocytes in adjacent bone as well as appositional growth onto, and penetration into, the material by new bone (Fig 8). Of note, and apparent in the specimens presented here (Figs 6 to 9), replacement of the mineral-organic adhesive by bone does not appear to take place through the action of osteoclasts, with no evidence of a front of material resorption with follow-on bone growth. Rather, new bone formation can be seen immediately adjacent to and within the body of the mineral-organic adhesive substance.

Therefore, the test material, the mineral-organic adhesive, clearly provided continued implant stabilization and, in fact, a stronger bond between bone and test material as healing progressed. Native bone replaced the test material without any loss of stability of the implant. In fact, the data demonstrate that the stability of the implant was slightly higher, but statistically similar, at 4 months to the control implant, which was only supported by native bone. In addition, and very importantly, the amount of new bone along the implant in the test sites (osseointegration) was similar to the amount of bone in the negative control sites, demonstrating that the turnover of the test material
did not interfere with native bone formation (Fig 12) and occurred without a cell-mediated resorption process. Furthermore, and different from the action of other bone grafts, the total amount of hard tissue integration to the implants in the mineral-organic adhesive sites was maintained from 10 days to 4 months; ie, as the mineral-organic adhesive is replaced by bone, it continues to adhere to the implant via its osseointegration-like bond (Fig 11).

A last major question was whether the test material could fill the defect space yet allow bone formation and replacement of the material over time without losing vertical height of the crestal bone. This is a common outcome that is monitored for the success of dental implants. The data from the histologic analyses clearly demonstrate that the test material and new bone are indeed present to the top of the implant throughout the healing period, up to the 4-month time point (Fig 10). In fact, in some histologic specimens, native bone formation occurs along the side, and over the top, of the mineral-organic adhesive. This is a remarkable finding considering that no cell or tissue exclusive materials or membranes or devices (such as meshes) were utilized in this study.

The limitations of this study are the number of animals studied and the relatively short period of observation. Thirteen additional animals are being followed for longer time periods to address aspects of this limitation and will be included in future publications. Preceding this study, there have been preliminary experimental studies of the material in various animals, including sheep, rabbits, and dogs. Additional studies, with differing protocols, are also either underway or planned to gain further insight into the strengths and limitations of this adhesive under varying clinical scenarios and for longer time periods of study. To the authors’ knowledge, no other bone cements or adhesives currently on the market, or under development, demonstrate the adhesive strength nor the rapid replacement with bone as demonstrated here.19,21,24

In conclusion, this study demonstrates, for the first time, that a novel mineral-organic adhesive can stabilize an implant placed in a site lacking primary stability, be replaced by native bone over time without the loss of structural support, and maintain the crestal bone to the top of the implant. The results with the test material were far superior to the use of a bovine bone graft material, which did not provide stabilization of the implant and demonstrated significantly less bone-to-implant contact formation over the 4-month course of healing. Because the mineral-organic adhesive material provides profound immediate stabilization with contact to the implant surface at the light microscopic level similar to native bone in a healed site, the mineral-organic adhesive provides osseointegration-like stability and represents a potential new treatment paradigm in implant dentistry. These results, taken together, suggest that the use of the test device in patients will greatly diminish the complexity, cost, and time of implant therapy in sites that lack bone around the implant.

CONCLUSIONS

Clinical application of the mineral-organic adhesive material at the time of implant placement immediately produces an osseointegration-like bond, with direct contact between the bone and the implanted adhesive. The mineral-organic adhesive hardens within minutes to produce a load-bearing level of stabilization of the implant, which increases over months as the material is replaced with bone. The authors propose the term “osseointegration-like” bond to signify this novel and unique primary implant stabilization by the mineral-organic adhesive.

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