

Norian Craniofacial Repair System: Compatibility with Resorbable and Nonresorbable Plating Materials

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Background: Choice of bone replacement materials is important when reconstructing large craniofacial defects. Hydroxyapatite cements are often used for such reconstructions. Recent advances in the development of these cements have produced locally applied, in situ hardening materials excellent for use in craniofacial defects. To date, there has been a paucity of data comparing the use of calcium phosphate cements in combination with titanium or resorbable plating systems and their combined biocompatibility. An experimental dog model was used to compare these systems.

Methods: Two 4 × 4-cm calvarial defects were created in each of 18 mongrel dogs, and defects were reconstructed with calcium phosphate cement with either titanium or resorbable mesh sheets to evaluate their interaction. Specimens were harvested and evaluated histologically for the development of new bone formation at 3, 6, and 12 months.

Results: At 3 months, no differences were noted in the amount of bone formed between titanium and resorbable plating. By 6 months, the resorbable mesh sheet showed delayed bone formation compared with the titanium mesh. At 12 months, bone formation over the resorbable mesh accelerated to be no different from the titanium mesh. Importantly, new bone formation was seen within the monocalcium phosphate cement Norian Craniofacial Repair System on a reliable basis, regardless of mesh plate used.

Conclusions: There are no long-term adverse effects with the use of Norian cement with either titanium or resorbable mesh. However, further studies need to be conducted to determine why there is an arrested healing phase between 3 and 6 months with the Norian cement and resorbable plating materials. (*Plast. Reconstr. Surg.* 120: 1487, 2007.)

There is still great difficulty associated with finding sufficient material with which to close large bone defects.^{1,2} Having a choice of a variety of well-tested bone repair materials is of vital importance when reconstructing structural craniofacial defects associated with congenital malformations, oncologic surgery, and posttraumatic defor-

mities. The preferred method for the repair of bone defects is still autograft.³⁻⁷ Free vascularized grafts are routinely used, with satisfactory results.⁸ However, allograft is still required for larger defects.⁹⁻²⁶ Currently, several different methods and a variety of materials are used to fill large defects. These include the use of preformed grafts from porcine or bovine tissues,²⁷ hydroxyapatite,^{28,29} and coral.^{30,31} Calcium phosphate cements are the second generation of hydroxyapatite bone substitutes. In the United States, at least four U.S. Food and Drug Administration–approved calcium phosphate cements have been developed for clinical use. More recently, chemically stable, monocalcium phosphate bone cement, Norian Craniofacial Repair System (Synthes Maxillofacial, West Chester, Pa.), has been used for surgical repair of bone defects.³²⁻³⁵

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When encountering large calvarial defects, physicians have noted that repair material must be supported by a framework of titanium or resorbable plates and screws as a scaffolding to keep the material from fracturing because of continued brain pulsations.³⁶ Chemical compatibility of the repair material with resorbable mesh and screws is being studied, and initial observations indicate that resorbable polylactic acid mesh may work better than polylactic acid membranes in supporting bioactive β -tricalcium phosphate.³⁷ It has yet to be determined whether polylactic acid mesh is more efficient than titanium mesh in stabilizing calcium phosphate cements. This study was aimed at evaluating the interactions between the acidic chemical breakdown products from polylactic acid-derived fixation materials and the Norian Craniofacial Repair System. The biocompatibility and effectiveness of this combination of materials will be compared with the Norian cement stabilized with titanium mesh in an experimental canine model.

MATERIALS AND METHODS

Animals and Surgical Procedures

Eighteen adult male mongrel dogs with an average weight of 29 kg (range, 23 to 34 kg) were used in this study. All animal care procedures and aseptic operations were performed in accordance with the requirements of the Institutional Animal Care and Use Committee at Medical City, which follow the guidelines for animal care stipulated by the National Institutes of Health. All animals received gentamicin preoperatively and postoperatively, 4 mg/kg subcutaneously twice daily, starting on the day of surgery and continuing until 10 days postoperatively. Anesthesia was induced with propofol, 4 to 8 mg/kg intravenously, and animals were then intubated and anesthesia maintained with isoflurane and oxygen. This was followed by administration of a one-time dose of glycopyrrolate (0.02 mg/kg) and the creation of bilateral 4 × 4-cm (16 cm²) craniectomies using aseptic technique (Figs. 1 and 2). Control defects were repaired with titanium 2.0-mm mesh sheets and screws (Synthes Maxillofacial). The experimental side was repaired with resorbable 2.0-mm mesh sheets and screws (Synthes Maxillofacial). The mesh plates were prepared such that they fitted the defect exactly and the edges of the mesh were parallel to the edges of the craniectomies, and a perpendicular flap was created to allow for screw placement. The mesh sheets were secured to



Fig. 1. Intraoperative photograph showing the size of the dual calvarial defects on either side of the sagittal suture. The defect on the left has a titanium mesh plate fixed in place, and on the right, there is a resorbable mesh plate. The Norian Craniofacial Repair System cement appears as a white paste packed on top of the mesh plates.

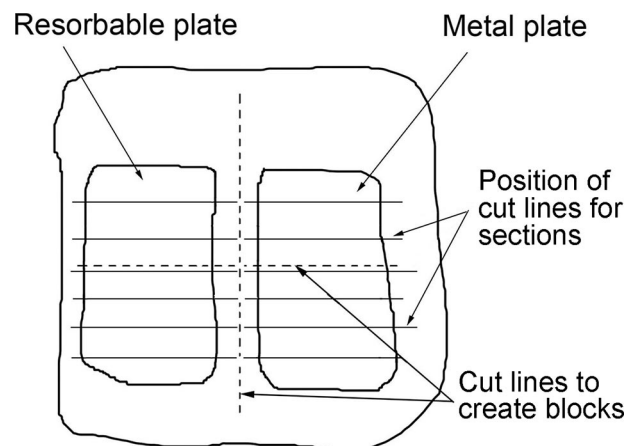


Fig. 2. Diagram showing the calvarial defects with metal and resorbable plates surrounded by host bone. The positions of the cuts to create four equal-sized blocks are shown as *dashed lines*. *Solid lines* show the position of the six cuts used to create the thick undecalcified sections for histomorphometry.

all edges of the defect. Once the trays were fixated, 8 ml of Norian cement for each defect was prepared according to the directions for use. Enough of the material was placed within each defect to fill the craniectomy flush with the periosteal surface, and the calcium phosphate cement was allowed to set (Fig. 1). Once the Norian cement set (approximately 10 minutes after application), the wounds were closed. Buprenorphine (0.005 mg/kg subcutaneously twice daily) was given for pain immediately postoperatively and then twice the follow-

ing day. The animals were transferred to the acute care facility at Medical City, where they were allowed to recover for 7 days, and then they were transferred to a long-term laboratory animal housing facility until they were euthanized for evaluation. The animals were divided into three groups of six dogs each. The first group was euthanized at 3 months, the second at 6 months, and the third at 12 months after surgery. All animals were euthanized by administration of 10 ml of 390 mg/ml of sodium pentobarbital intravenously (120 mg/kg) according to American Veterinary Medical Association guidelines.³⁸

Tissue Collection and Data Analysis

After gross examination of the surgical site and removal of the overlying scalp, the defects were photographed. Inflammatory changes in all groups were subjectively reported. The calvariae were then removed en bloc from the dogs and placed in 10% buffered formalin. After a week of fixation, each calvaria was cut in half in a sagittal plane, and each half was then cut into four equal-sized blocks (Fig. 2). Each block was embedded in methylmethacrylate, with the surface showing the greatest bone/mesh sheet contact area presented for sectioning. Six thick sections were cut from each specimen with an IsoMet low-speed saw (Buehler, Ltd., Lake Bluff, Ill.). Each thick section was then ground down and the ground sections stained with methylene blue to reveal soft tissues, and with van Gieson picrofuchsin to reveal mineralized tissue. Under the microscope, titanium mesh appeared black, whereas the resorbable mesh appeared as unstained blank areas with

straight edges, butted up against blue-stained soft tissue. The specimens were measured under a 20- μ m gridded graticule in a 10 \times magnification eyepiece (Edmund Industrial Optics, Barrington, N.J.). New bone growth was evaluated and the thickness measured at the junction of the calcium phosphate cement, plating material, and native bone (Fig. 3). Scores for new bone growth were given for both the dural and the periosteal sides of the calvarial specimens. For these evaluations, three separate reviewers scored the specimens.

Statistical Analysis

Results were tabulated and expressed in millimeters as the mean \pm SD. Statistical analysis was performed on all groups with intergroup comparisons using a one-way analysis of variance with Tukey-Kramer post hoc test for significance at each time point. An α level of 0.05 or less was considered significant. Analysis of variance assumes that the sample population is normally distributed, has equal variance, and is mutually independent. As the defects were discrete from each other with no potential for or evidence of crossover effects, the treatment given to each defect was mutually independent. Inflammatory changes in all groups were analyzed using chi-square evaluation, and an α level of 0.05 or less was considered significant.

RESULTS

All 18 animals survived their respective timelines. In the 3-month group, one animal developed an open fistula on the experimental side, and one other animal developed cellulitis over the

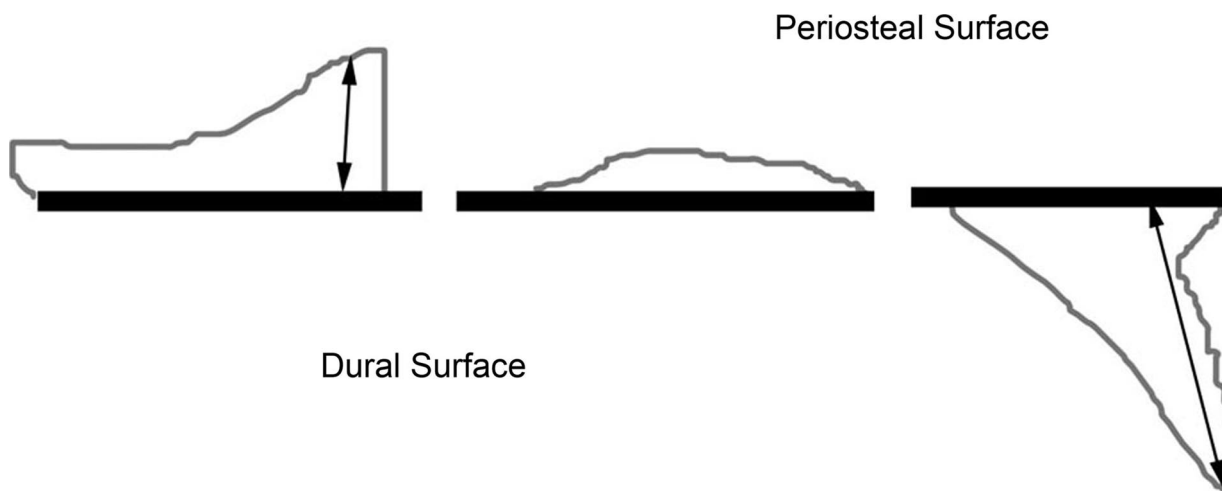


Fig. 3. Diagrams showing the measurement of maximum bone thickness on the periosteal and dural surfaces of the defects. The plate is shown as a thick black line, with new bone outlined in gray. Arrows show the position of the measurements.

incision site that was treated with oral antibiotics. The animal with the draining fistula was noted to have complete separation between the Norian cement and the resorbable mesh at necropsy. Two animals in the 6-month group also developed localized skin infections over the incision site and were treated with oral antibiotics until necropsy. One animal in the 12-month group was treated for a chronic surgical site infection. Overall, this represented a 22.5 percent infection rate.

During processing of the specimens after necropsy, the calvaria from one animal in each group did not appear on gross examination to have enough reliable bone to be graded. The calvariae were from the 3-month animal with the fistula and one animal each in the 6-month group and the 12-month group with infection. These three animals were removed from histologic analysis. The

calvariae from the remaining 15 animals, five in each group, were examined histologically. This represented a total of 30 specimens, 15 with titanium and 15 with resorbable mesh.

3-Month Animals

Gross analysis of the craniectomies at 3 months after surgery showed integration of the newly formed bone to the edges of the defect (Fig. 4). The periosteal surface showed no gross differences in the Norian cement overlying either the titanium or resorbable mesh sheet. In those specimens where the dura mater was still intact after resection, good association of the dura with the overlying materials was observed in all groups. On gross manipulation, the resorbable mesh was non-malleable in all cases.

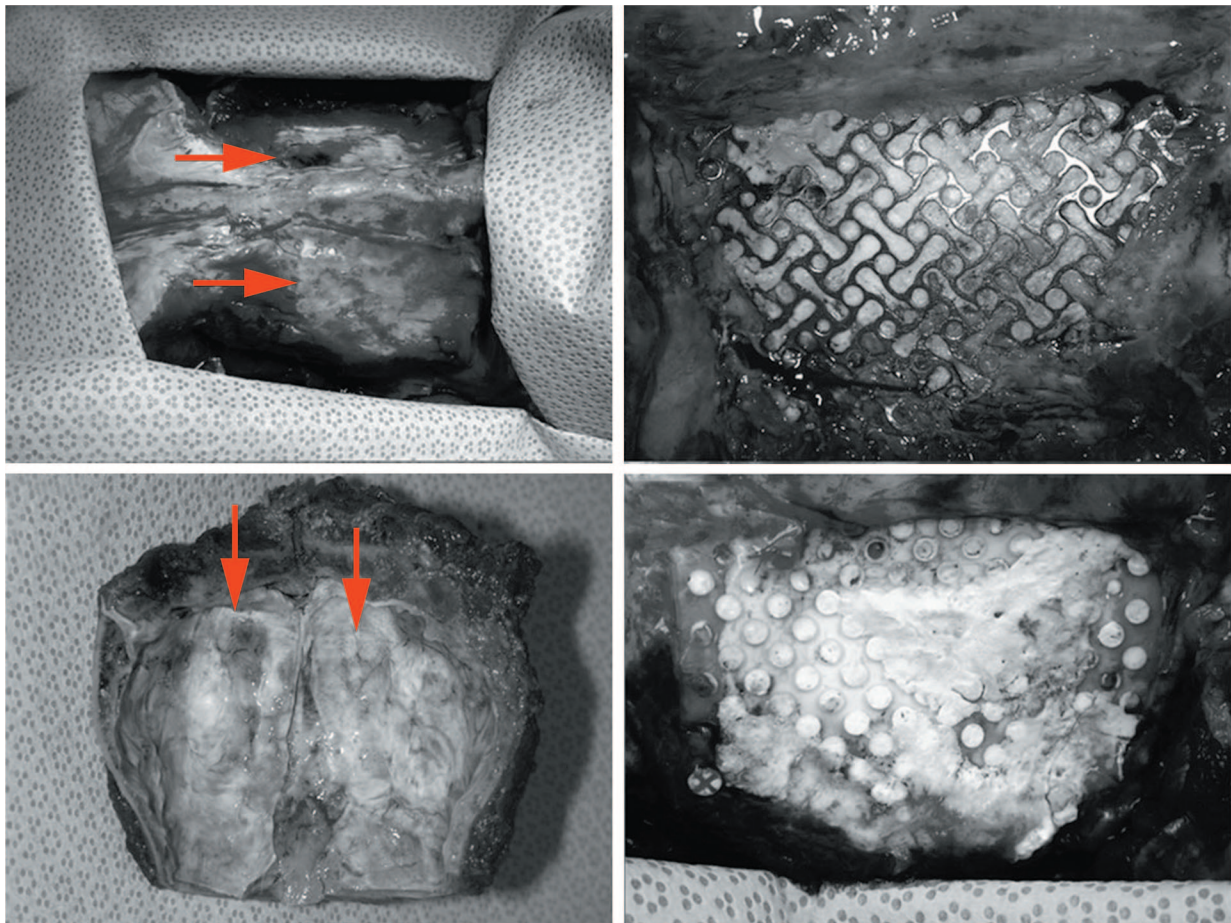


Fig. 4. Defects at tissue harvest at 3 months. (Above, left) Periosteal view in situ, with the position of the defects indicated by arrows. (Above, right) Defect repaired with titanium mesh, with periosteum reflected to show Norian cement within the mesh grid. (Below, left) Endocranial view of calvaria showing close attachment of dura mater to the Norian cement and mesh in both defects. Arrows indicate the border of each defect. (Below, right) Defect repaired with resorbable mesh, showing Norian cement within the intact mesh grid.

Table 1. Analysis of Bone Measurements

Time	Plate	Dural Measurement (mm ± SD)	<i>p</i>	Periosteal measurement (mm ± SD)	<i>p</i>
3 months	Titanium	0.47 ± 0.63	NS	0.18 ± 0.2	NS
	Resorbable	0.44 ± 0.74		0.17 ± 0.13	
6 months	Titanium	1.57 ± 0.92	<0.001	0.35 ± 0.35	NS
	Resorbable	0.30 ± 0.39		0.15 ± 0.08	
12 months	Titanium	0.88 ± 0.23	NS	0.22 ± 0.22	NS
	Resorbable	1.07 ± 0.4		0.46 ± 0.28	

NS, not significant.

The histomorphometric measurements of the thickness of the bone along the dural surface were 0.47 ± 0.63 mm for the craniectomies fixed with the titanium mesh and 0.44 ± 0.74 mm for the craniectomies fixed with the resorbable mesh (Table 1). This difference was not significant. Measurements of bone thickness on the periosteal surface were 0.18 ± 0.2 mm for the titanium mesh

group and no different from the measurements for the resorbable mesh group (0.17 ± 0.13 mm).

6-Month Animals

Gross analysis of the craniectomies at 6 months after surgery showed integration of the newly formed bone to the edges of the defect (Fig. 5). The

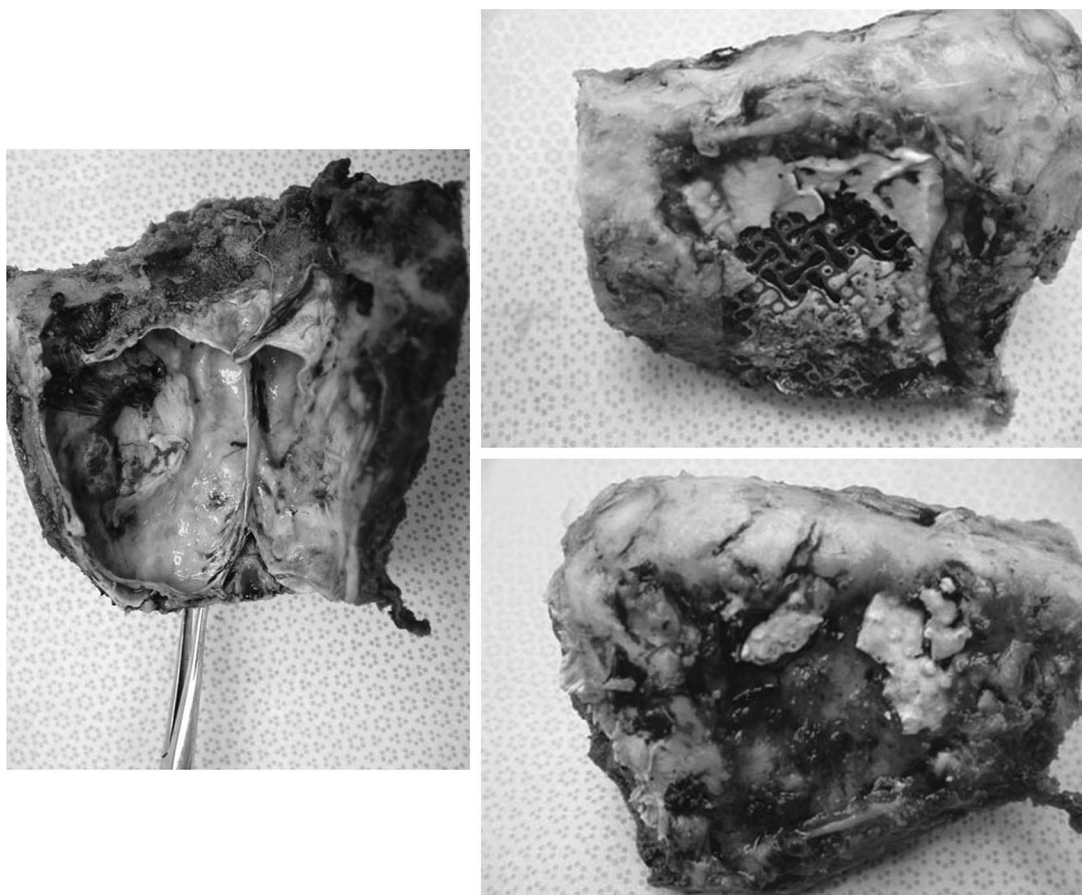


Fig. 5. Defects at tissue harvest at 6 months. (Left) Intracranial view, showing close association of the dura mater with the defects. A tear in the dura in the defect on the left was created during removal of the calvaria. (Above, right) Defect repaired with titanium mesh, with periosteum reflected. Note the large amount of intact Norian cement within the mesh. (Below, right) Defect repaired with resorbable mesh. Note the Norian cement broken into pieces and the transparent appearance of the resorbable mesh.

Norian cement was present in both the titanium and resorbable mesh–repaired defects. However, the Norian cement in the resorbable mesh group was less intact than that seen at 3 months, and the mesh had a more transparent appearance. In the specimens where the dura mater was intact after resection, good association of the dura with the overlying materials was observed in all groups. This is also similar to the findings for the 3-month group. However, on gross manipulation, the resorbable mesh was becoming malleable in all cases.

The histomorphometric measurements of bone thickness at the dural surface were 1.57 ± 0.92 mm for the titanium mesh group and 0.3 ± 0.35 mm for the resorbable mesh group (Table 1). This difference was significant ($p < 0.001$). The bone thickness at the periosteal surface was 0.35 ± 0.35 mm for the titanium mesh group and 0.15 ± 0.08 mm for the resorbable mesh group, a difference that was not significant.

12-Month Animals

Gross analysis of the craniectomies at 12 months revealed good integration of the newly formed bone with the host bone in both the titanium and resorbable mesh groups. The appearance of the Norian cement and mesh appeared similar to that described for the 6-month group (not shown). On gross manipulation, the resorbable mesh appeared more malleable than it did at 6 months. Good contact between new bone and titanium, and new bone and Norian cement was noted in the titanium mesh group (Fig. 6). However, in the resorbable mesh group, new bone did not make contact with the resorbable mesh, and was only found in direct contact with the Norian cement. In the titanium-plated group, soft tissues with good cellularity resembling periosteum were noted surrounding the titanium mesh (Fig. 6, *left*). However, in the resorbable mesh groups, the soft-tissue matrix surrounding the mesh was disrupted and acellular (Fig. 6, *right*). No localized inflammatory reaction around the resorbable mesh was noted in any of the groups. The bone thickness at the dural surface was 0.88 ± 0.23 mm for the titanium mesh group and 1.07 ± 0.4 mm for the resorbable mesh group (Table 1). The bone thickness at the periosteal surface was 0.22 ± 0.22 mm for the titanium mesh group and 0.46 ± 0.28 mm for the resorbable mesh group. Neither of these differences was significant.

DISCUSSION

When repairing large calvarial defects, two major issues must be addressed when looking for repair materials. First, materials need to be chosen that will result in sufficient bone formation to cover the defect. Second, although not less important, it is necessary to choose materials based on how soon they have to be load bearing (or at least resistant to deformation). When very large defects need filling, bone void fillers are required, and several calcium phosphate cements have been used. These materials are biocompatible and osteoconductive.^{34,39} However, these materials were prone to fracturing and required a supporting framework to stabilize the material in the defect.³⁶ The advantage of using titanium mesh for support is that they provide immediate and permanent stability, are osteoconductive, and become osseointegrated into the new bone. One problem is that the mesh will not alter shape, which is a disadvantage in situations where bone remodeling will occur, as in growing skulls of young children. This requires surgical removal of the titanium mesh. More recently, several resorbable polylactic acid plating materials have become available. These meshes have the advantage of providing good scaffolding and early stiffness and do not need to be removed. However, there are indications that breakdown of these resorbable materials may be inhibitory to bone formation, and they may not provide long-term stability to the healing defect.^{36,40–45}

The present study compared the amount of bone formation occurring when resorbable or titanium mesh was used to stabilize monocalcium phosphate bone cement (Norian Craniofacial Repair System). Bone healing was compared by histomorphometric analysis, and mesh stability was compared qualitatively by gross manipulation at 3, 6, and 12 months. New bone formation at the dural and periosteal surfaces was noted in all groups at all time points. Although new bone was noted throughout the defect, most new bone was being appositionally deposited against the implanted materials, with some invasion of the calcium phosphate by bone. Bone formation at 3 months was significantly greater at the dura than at the periosteum in the titanium-plated group, but not the resorbable plating group. New bone formation in the titanium plated group peaked at 6 months and remained unchanged thereafter. Bone formation in the resorbable plating group was significantly delayed compared with the titanium-plated group at 6 months but showed similar

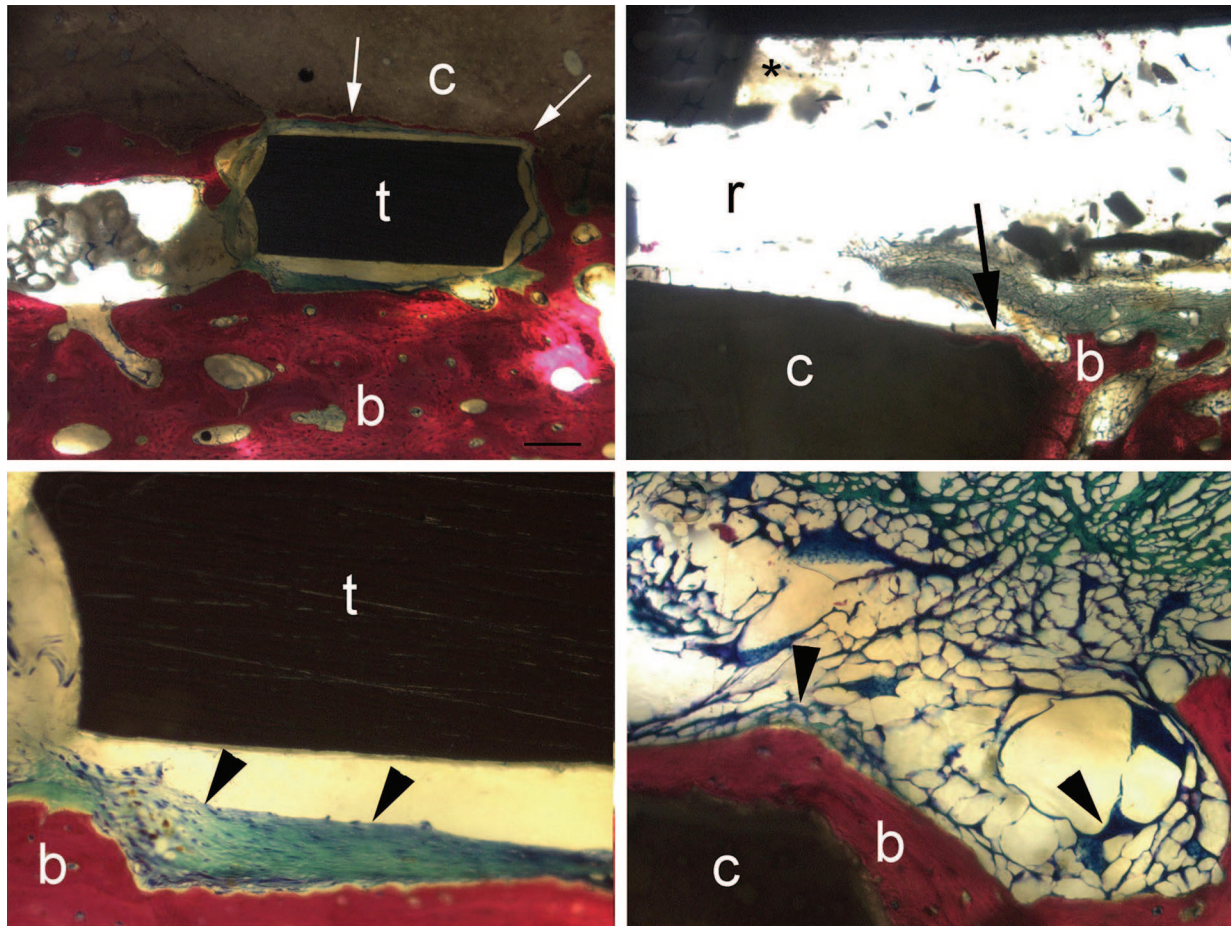


Fig. 6. Histologic sections through undecalcified bone of specimens harvested at 12 months. (Above, left) Low-power image of a titanium-repaired defect showing thick bone on the dural surface and the thin rim of bone completely encircling the titanium (arrows). (Above, right) Low-power image of a resorbable mesh–repaired defect showing a thin rim of bone on the surface of the Norian cement, with a complete absence of bone along the resorbable mesh surface (asterisk). (Below, left) High-power image of above, left, showing the presence of an intact periosteum on the bone surface abutting the titanium plate (arrowheads). (Below, right) High-power image of above, right, showing the disorganized and acellular matrix on the surface of the bone abutting the resorbable plate (arrowheads). b, bone; c, Norian Craniofacial Repair System; r, resorbable mesh; t, titanium mesh. Bar = 400 μ m.

levels of bone formation compared with the titanium group at 12 months. This is similar to the finding of McGinnis et al.⁴⁶ and Nasser et al.,⁴⁷ who showed delayed bone formation in defects fixed with resorbable versus nonresorbable meshes. The delayed bone formation noted in the resorbable mesh group was likely attributable to the increased mobility induced by the breakdown of the resorbable mesh, also resulting in resorption of the cement. These results concur with those of Eppley and Sadove,⁴² who showed healing of the bone against defects fixed with either titanium or resorbable meshes. However, unlike the Eppley and Sadove findings, the resorbable mesh was still present in the cranial

defects at 1 year. This difference was likely attributable to (1) the difference in animal model used, as the Eppley and Sadove study used a rabbit model; and (2) the type of resorbable polymer used in plating, because Eppley and Sadove used fast-resorbing LactoSorb (Biomet Microfixation, Jacksonville, Fla.).

Interestingly, although good bone formation could be seen against the Norian cement and surrounding the titanium mesh, little to no bone formation was noted in the proximity of the mesh. This appeared to be attributable to a localized disruption of the soft tissues in contact with the resorbable mesh, with an absence of cellularity in the soft tissues. Although this re-

action appeared to be a necrotic reaction, no evidence of inflammatory cells was noted in the areas of disrupted tissue. All inflammation reported was noted at the site of wound closure. The high percentage of infection was likely attributable to stress on the wound closure caused by the massive size of the defect created by two osteotomies, one on either side of the sagittal suture. It is important to note here that although there appeared to be some inhibition of bone formation surrounding the resorbable mesh, this inhibition was not associated with infection and did not extend to the Norian cement. Because the infection did not extend into the defect, no further culture or examination of the infected tissue was carried out. Good bone formation was seen surrounding and within the Norian cement in both the titanium and resorbable mesh-plated groups.

The resorbable mesh showed increased malleability at 6 months, compared with the 3-month group and compared with the titanium-plated groups. However, the malleability was not marked and would be in agreement with the observations of Wiltfang et al.,⁴⁸ who concluded that the mechanical properties were sufficient for creating stability within craniofacial surgical defects. One rationale for placing the plating system under the bone cement is that the mesh provides a barrier against the dural pulsations, which may be responsible for breaking up the bone cement within the defects. Similar to the findings of Losee et al.⁴⁹ and Pang et al.,⁵⁰ this study found that placing the mesh under the cement resulted in good bone formation at the dural surface, against the cement squeezed through the mesh gaps. The question remains whether similar or greater bone formation could be induced if the plating systems were placed over the top of the cement.

CONCLUSIONS

On the basis of the results of this study, the use of the Norian Craniofacial Repair System and titanium mesh together appears to be appropriate for both short- and long-term stability and bone formation. Bone formation associated with Norian cement in the resorbable plating groups appears similar to that in the titanium plating groups at 12 months but was delayed compared with this group at 6 months. This finding, along with the increased malleability of the resorbable mesh at 6 months would suggest that this combination not be used where early stability and accelerated bone formation are desired. However, this combination may

be appropriate for good long-term outcomes where early stability is not an issue.

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DISCLOSURE

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article.

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