Multiple-suture nonsyndromic craniosynostosis: early and effective management using endoscopic techniques

Clinical article

DAVID F. JIMENEZ, M.D., AND CONSTANCE M. BARONE, M.D.

Department of Neurosurgery, The University of Texas Health Science Center at San Antonio, Texas

Object. The authors present the results of treating infants with multiple-suture nonsyndromic craniosynostosis in whom the authors used minimally invasive endoscopy-assisted techniques and postoperative cranial molding over an 11-year period.

Methods. A total of 21 patients who presented with multiple-suture (nonsyndromic) craniosynostosis were treated using minimally invasive endoscopy-assisted craniectomies. Surgery was followed by treatment with custom-made cranial orthoses for up to 12 months. A total of 48 sutures were treated. The most common was the coronal suture (38 cases) and this was followed by the sagittal (11 cases), metopic (6 cases), and lambdoid (3 cases) sutures. There were 13 male and 8 female pediatric patients. Their ages ranged between 3 weeks and 9 months (mean 3.2 months, median 2.5 months). The sagittal suture was treated with a wide vertex craniotomy via 2 incisions located behind the anterior fontanel and in front of the lambda. The metopic suture underwent a suturectomy as did the coronal and lambdoid sutures.

Results. The mean follow-up duration was 61 months (range 3–135 months). There were no deaths. In patients with bicoronal synostosis, brachycephaly was corrected. Patients presenting with vertical dystopia or nasal deviation had these deformities corrected as well. The mean blood loss was 42 ml (range 10–120 ml). The mean hospital length of stay was 1 day. The intraoperative transfusion rate was 0%. The results indicate that nonsyndromic multiple-suture synostosis can be safely and effectively treated using endoscopic techniques.

Conclusions. Early treatment of complex multiple-suture synostosis with endoscopic techniques provides an excellent surgical alternative. The results of the present study indicate marked correction of skull base and craniofacial deformities. Endoscopy provides a safe and effective way to treat these patients.

(Key Words: craniofacial; suture; synostosis; endoscopy)

Abbreviation used in this paper: EBL = estimated blood loss.)

Neurosurgeons and craniofacial plastic surgeons typically face difficult and vexing challenges when treating patients with single-suture synostosis. This problem is proportionately compounded as the number of synostoses increases in a single patient. Aside from the disproportional and compensatory cranial growth that occurs with single-suture involvement, multiple-suture synostosis additionally leads to complex skull base deformities, increased intracranial pressure, orbitocranial abnormalities, and misalignment as well as not yet fully understood psychological problems. Two of the most challenging questions relate to the type of surgery that should be performed in an infant newly diagnosed with multiple-suture synostosis, as well as the best timing of the recommended procedure. In our experience with surgery in older children (1 year of age), the application of conventional calvarial remodeling techniques has been associated with inconsistent results and suboptimal long-term outcomes.

Given the excellent long-term results that our center has achieved treating young infants with single-suture synostosis,1–13,22 we decided to alter our treatment protocol and began treating infants with nonsyndromic (phenotypic) multiple-suture calvarial synostosis using the same principles of minimally invasive endoscopy-assisted craniectomies followed by postoperative cranial orthotic treatment. We present our experience of consecutively treating those patients during the past 11 years. During the study period, all patients presenting with nonsyndromic multiple-suture synostosis (excluding
patients with Apert, Crouzon, Pfeiffer syndrome, and the like) and who were under 6 months of age were selected for endoscopic treatment. In all patients head CT scans had been obtained, and these were carefully analyzed for sutural synostosis. Once phenotypic syndromic characteristics were ruled out (for example, broad thumbs and polydactyly), the patients were selected for endoscopic suturectomies.

**Methods**

Twenty-one patients, ranging in age from 3 weeks to 9 months, presented to our craniofacial center with craniosynostosis involving more than one calvarial suture. There were 13 male and 8 female pediatric patients. These individuals were selected from among a larger group of patients with multiple synostoses because they did not have any of the phenotypical features of a well-known syndrome. Forty-eight sutures were involved and the most commonly affected suture was the coronal suture (38 cases) followed by the sagittal suture (11 cases), the metopic suture (6 cases), and the least involved, the lambdoid suture (3 cases). The first patient underwent surgery in January of 1998 and the last in March 2009. The follow-up duration ranged from 3 to 135 months (mean of 61 months) (Table 1). Following surgery, head scans were obtained using the Star Scanner (Orthomerica). The data were used to manufacture a custom-made helmet of Surlyn (DuPont), a strong polymer with excellent molding and durability characteristics. The goal was to redirect cranial growth and achieve normal head shape and size. For instance, in patients with bicoronal synostosis, pressure was applied on the temporal and parietal areas while allowing forward growth of the forehead, thereby decreasing the patient’s cephalic index. The helmet was worn continuously, except for bathing or cleaning the infant’s head. Head circumference measurements were closely followed to ensure that normal and proper brain growth took place without restriction. Cephalic index measurements (euryon-to-euryon distance ÷ opisthocranion-to-glabella distance × 100) were taken preoperatively and at each postoperative visit. Measurements were made both with calipers and also corroborated with Star Scanner measurements. All data were collected and entered into a prospectively created, comprehensive database.

### Surgical Techniques

**Anesthesia.** Standard anesthetic monitoring techniques were used, including electrocardiography, noninvasive blood pressure monitoring, pulse oximetry, precordial Doppler ultrasonography, and temperature monitoring. Induction of general anesthesia was accomplished with inhalation of sevoflurane with oxygen and nitrous oxide. Muscle relaxation was achieved by using rocuronium at a dose of 600 mg/kg. Corneal protection was provided by corneal shields and ophthalmological ointment. A single intravenous dose of an antibiotic was given prior to starting the surgical procedure. A broad-spectrum antibiotic (cefazolin 50–60 mg/kg) was used. To help with postoperative pain control, rectal acetaminophen (10–15 mg/kg) was also administered prior to beginning the procedure. At the conclusion of the surgery, anesthetic agents were discontinued and muscle relaxant reversal agents were administered as necessary. Additional fentanyl and morphine were administered for pain control. Extubation was performed when the patient met the standard extubation criteria.

**Positioning.** In most cases, patients were placed supine on a cerebellar headrest. Those with bicoronal involvement were placed with the head midline and the neck slightly flexed. The same position was used when the metopic suture was involved. Involvement of both lambdoid sutures required placement of the patient prone on the cerebellar headrest with adequate ocular protection. With unilateral lambdoidal involvement, the patient was supine with the head rotated at 90° to the contralateral side. Whenever there was involvement of the sagittal suture, the modified prone (sphinx) position was used to gain access to the anterior and posterior aspects of the cranial vault.

**Incisions.** Access to a stenosed coronal suture was gained with a 2 to 3-cm incision located over the coronal suture at the level of the stephanion. Subgaleal dissection was done between the anterior fontanel and the squamosal suture behind the pterion. The metopic suture was reached utilizing a single 2 to 3-cm incision located over the metopic suture behind the hairline and in front of the anterior fontanel with subgaleal dissection between the nasofrontal suture and the anterior fontanel. The lambdoidal suture was accessed with two 2 to 3-cm incisions. One incision was made over the suture immediately lateral to the lambda, and the other was made, also over the suture, immediately medial to the asterion. Finally, the sagittal suture was reached via 2 incisions. The first was made over the anterior fontanel and the second was made immediately in front of the lambda. The dissection plane was developed between the galea and pericranium, using monopolar electrocautery (needle tip) set at 15 W. Thus, the loose areolar tissue was separated in a completely bloodless fashion.

### Craniectomies

A pediatric 7-mm craniotome was
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used to create a bur hole at each incision. The bur hole was enlarged longitudinally along the suture axis when the coronal, metopic, and lambdoid sutures were involved. In the case of sagittal involvement, the bur hole was placed at the lateral edge of the incision and an osteotomy was carried across the midline to the other side, to a symmetrical distance from the suture. Enlargement and elongation of the bur hole allowed the introduction of a 4-mm rigid 30° angled endoscope into the epidural space for visualization and dissection of the space with a 7 Fr insulated suction tube. The dura mater was fully dissected from the overlying bone from the anterior fontanel to the nasofrontal suture (metopic), squamosal suture behind the pterion (coronal), or lambda (sagittal). In the case of lambdoid involvement, epidural dissection was undertaken between the lambda and asterion. Removal of bone was done with a combination of angled Kerrison rongeurs, bone (pituitary type) rongeurs, and Mayo scissors. The cranietomy size for the metopic, coronal, and lambdoid sutures averaged 7 mm (range 5–10 mm), and 50 mm (range 40–60 mm) for sagittal involvement. Osseous hemostasis was easily obtained using a suction-monopolar unit (Valley Lab) set at 60 W. The bone was cauterized under direct visualization until all oozing and bleeding was stopped. The incisions were closed with 4-0 Monocryl (Ethicon, Inc.), and the dermis was sealed with Ethibond (Ethicon, Inc.).

Postoperative Treatment. The patients were admitted to the inpatient unit for overnight observation and discharged the following morning. They underwent scanning (Star Scanner Orthomerica) on the 4th postoperative day and baseline anthropometric measurements were obtained. A custom-made Surlyn helmet was manufactured, delivered, and fitted on the 6th postoperative day. The first helmet was worn for about 6–8 weeks, and subsequent helmets were made as the child’s head grew and changed in shape. Helmet therapy lasted between 10 and 12 months. After the 1st year following surgery, the patients were followed on an annual or biannual basis.

Results

Operative times ranged from 38 to 157 minutes (mean 83 minutes). The hospital length of stay for all but one patient was 1 day. One patient stayed for 3 days due to history of prematurity and apneic episodes. The estimated blood loss ranged from 10 to 120 ml (mean 42 ml). The estimated percentage of blood volume lost ranged from 3.5 to 27% (mean 9%). There were no intraoperative blood transfusions, and 2 patients required non–life-threatening blood transfusions (80 and 100 ml). The width of the cranietomy ranged between 0.4 and 6.5 cm (mean 2 cm) and the length ranged between 5 and 12 cm (mean 9.6 cm). Two patients experienced small class II clinically insignificant venous air embolisms. The mean preoperative hematocrit levels were 30, 25, and 23 preoperatively, immediately after surgery, and 1 day postoperatively (Table 2). There were no intra- or postoperative deaths. There were no postoperative hematomas or infections. One patient with bicoronal synostosis had a dural tear and small cortical injury. Postoperatively, she developed a subgaleal CSF collection that required a second procedure to repair the leak, which had no untoward effects. There were no problems associated with the use of helmets, and there were no injuries to the sagittal or transverse sinuses. One patient had a persistent small area of nonossification along the cranietomy of the coronal suture, but no further surgical intervention has been required.

In the 3 patients who presented with vertical dystopia, the symptom resolved (Fig. 1) and nasal deviation was corrected. In the patients with bicoronal synostosis and brachycephaly, the cephalic indices decreased an average of 26%. Antimongoloid orbital slant was corrected to produce a normal orbital alignment as well as the bitemporal

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* EPBVL = estimated percentage of blood volume lost; LOS = length of stay.

Fig. 1. Case 1. A 6-week-old girl with left coronal, sagittal, and left lambdoid craniosynostosis. Her deformational compensatory growth changes consist of marked calvarial deviation to the right, vertical dystopia, hypertelorism, nasal deviation, and cranial scoliosis.
widening seen with brachycephaly (see Fig. 9). Helmet therapy following release of the stenosed coronal sutures led to internal distraction and forward movement of the naso-orbital complex (see Fig. 8). So far, it has not been necessary to perform bifrontal orbital advancement in our patients due to proptosis or corneal compromise.

Longitudinal analysis of the entire cohort’s head circumference demonstrated that all of the patients’ measurements followed standard population isocurves appropriate for each patient. As such, it was evident that there were no cases in which head or brain growth was restricted. Furthermore, analysis also indicated that proportional growth occurred. The mean preoperative cephalic index was 98 (range 82–111) and the median was 97. Late postoperative cephalic index (≥ 1 year) was 83 (range 79–92) and the median was 82. Overall, there was a 15% decrease from preoperative baseline.

Helmet therapy was continued on an average for 11 months postoperatively (range 10–12 months). The decision to discontinue therapy was based on the child’s reaching the 12-month postoperative mark or 18 months of age. It was concluded, from previous experience with other patients, that with brain growth plateauing at 18 months (head circumference increases by 2 cm in 4 weeks in patients <3 months of age vs 2 cm in 18 months in those age 18 months), further helmet usage does not provide significant additional head molding. Furthermore, it was noticed that progressive, albeit slow, changes continue to occur long after helmet therapy discontinuation. As such, it was believed that no further helmet treatment was needed after 12 months.

Illustrative Cases

**Case 1**

This 6-week-old girl presented with marked cranial and facial deformities and rapidly progressive disfigurement (Fig. 1). Thin-slice CT scanning demonstrated premature closure of the left coronal, left lambdoid, and sagittal sutures. Careful assessment revealed all other calvarial and skull base sutures to be patent. Given the patient’s young age and the rapid progression of her deformities, we decided to proceed with craniectomies of the involved sutures with the primary intent of halting progressive deformation and performing definitive treatment with conventional calvarial vault remodeling techniques at a later stage.

The patient was taken to the operating room and placed supine with the head fully rotated to the right on a cerebellar headrest. Two single intravenous lines were inserted by the anesthesia team following induction of general anesthesia. No arterial or central venous lines or Foley catheters were used. Following skin preparation with povidone-iodine solution and intravenous Ancef, the 3 scalp incisions were made. One incision was made at the anterior fontanel, a second incision at the lambda, and a third at the left asterion. Under endoscopic guidance, the subgaleal spaces were dissected from anterior fontanel to the left pterion, anterior fontanel to the lambda, and from the lambda to the left asterion. A 1-cm craniectomy was made from the asterion to the lambda, and another 1-cm craniectomy was created from the pterion to the anterior fontanel. A 4-cm craniectomy was made between the anterior fontanel and the lambda, and all of these were connected to form a C-shaped craniectomy, which incorporated all 3 involved sutures (Fig. 2). Hemostasis was obtained as previously described and followed by standard galeal and dural closure. Postoperatively, the patient was treated with molding helmets, which applied pressure over the areas of overcompensated growth while allowing additional space in areas of deficient and retracted growth.

The surgical procedure lasted 150 minutes, the EBL was 50 ml, and there was no need for intra- or postoperative blood transfusions. There were no venous air emboli; dural tears; intraparenchymal brain injuries; sagittal sinus transverse or sigmoid sinus injuries; infections; postoperative hematomas; or hemodynamic instability. The patient was discharged from the hospital the morning following surgery, and helmet therapy was initiated on the 6th postoperative day. The patient was closely followed during the 1st year and annually during the next 7 years (Fig. 3).

Very early in the treatment process it became evident that our goal of halting her progressive deformity was achieved. Moreover, to our pleasant surprise, it was noted that the deformities began to correct during the early months after surgery. Her cranial vault expanded to the right side, obtaining cranial symmetry. The nasal deviation corrected and the vertical dystopia corrected almost completely over time. Preoperative CT scans acquired through the skull base showed significant deviation of the longitudinal axis of the foramen magnum in relation to the nasal septum (Fig. 4A), which began to correct at 2 years (Fig. 4B) and completely corrected at 6 years (Fig. 4C). Correction of the orbital misalignment and dystopia, as well as straightening of the nasal bones, was documented radiographically (Fig. 5A and B). Due to the major restrictive growth of the calvaria on the left side, the compensatory brain growth on the right side led to marked gyral markings and skull indentation, which fully corrected without direct surgical intervention (Figs. 5C and 6). Her psychological and cognitive development are normal, and she is currently an honors student with excellent memory and academic skills.

**Case 2**

This 9-week-old girl presented with synostosis of the metopic and right coronal sutures, which led to vertical dystopia, nasal deviation, frontal deviation, asymmetrical trigonocephaly, and right ocular proptosis (Fig. 7A). Like the patient in Case 1, she suffered rapidly progressive deformational changes, which led us to recommend endoscope-assisted craniectomies of the involved sutures to halt the progression and, later, treatment. The patient was taken to surgery, and following induction of general anesthesia and placement of only 2 intravenous lines, she underwent resection of the metopic and right coronal sutures. The metopic suture was accessed via a small incision over the forehead and the coronal suture, with an incision over the right stephanion as previously described. The metopic suture was resected in its entirety from the anterior fontanel to the nasofrontal suture and the coro-
nal suture from the fontanel to the right pterion. The total operative time was 90 minutes, EBL was 15 ml, and each craniotomy was approximately 1 cm in width. There was no evidence of venous air embolism with precordial Doppler monitoring. The patient did not require intra- or postoperative blood transfusions. There were no dural tears or injury to the brain or venous sinuses. The patient was observed overnight and discharged from the hospital the following morning. Likewise, postoperatively, she was treated with helmet therapy for about 12 months. During the 1st year after surgery, it became evident that not only were the progressive deformities halted but her skull base and cranioorbital deformities were corrected (Fig. 7B). Her nasal deviation, trigonocephaly, plagiocephaly, and vertical dystopia showed marked and significant correction by 2 years (Fig. 7C). Her cognitive development was normal, and she has not exhibited difficulties in reaching all age-appropriate milestones.

**Case 3**

This 10-week-old boy presented with bicornoral craniosynostosis but no phenotypic evidence of an associated syndrome such as Pfeiffer, Crouzon, or Apert. He had a significantly diminished anterior cranial fossa vault volume with marked frontal bossing, brachycephaly, and depressed and recessed nasal-zygomatic-frontal complex (Fig. 8 left). He was taken to surgery for release of his stenosed sutures with endoscopy-assisted craniectomies. Following general anesthesia induction, 2 peripheral intravenous lines were inserted; there was no need for central venous or arterial lines. The right coronal suture was approached via a 2-cm incision at the stephanion, and as previously described, a 1-cm strip of bone was resected, extending from the anterior fontanel to the pterion. The contralateral sutures were approached in similar fashion, again without complication. There were no dural tears, brain injuries, or venous sinus injuries. The EBL was 50 ml. The width of the cranectomy was 7 mm on both sides. No blood was transfused either intra- or postoperatively, and there were no venous air emboli, hematomas, or CSF leaks. The patient was observed overnight and discharged home the morning following surgery. Helmet

**Fig. 2.** Case 1. Artist's rendition of the treatment and outcome in the patient with coronal, sagittal, and lambdoid craniosynostosis. The upper left inset shows preoperative dystopia and other compensatory changes. The upper right inset shows the extent of osseous resection and the endoscopic approach. The lower right inset shows aerial view of the patient’s head preoperatively and the amount of bone removed during surgery. The lower left inset demonstrates cranial expansion and normalization while the helmet is still worn. The center image shows almost complete normalization of the craniofacial skeleton at 1 year of age.
Fig. 3. Case 1. Series of anteroposterior, lateral, and top views extending from presurgery and sequentially taken to a 7-year follow-up after endoscopy-assisted craniectomies of the involved sutures and postoperative cranial helmet therapy. All of the deformities have corrected by 1 year of age and remain unchanged at the 7-year follow-up.

Fig. 4. Case 1. Axial CT scans obtained over the years. A: Preoperative CT scan taken through the skull base and foramen magnum. A line drawn along the nasal septum intersects a line drawn along the longitudinal axis of the foramen magnum at 17°. This significant skull base deviation was a direct result of premature closure of the 3 calvarial sutures. B: Scan taken 2 years after surgery showing that the skull base deviation has significantly decreased from 17 to 10°. C: At 6 years, complete realignment of the skull base is apparent. The line drawn along the septum bisects the longitudinal axis of the foramen magnum. The preoperative deformities caused by the synostoses were completely corrected by the growing brain once the sutures were released, indicating that skull base morphology is driven by a normally growing brain.

Fig. 5. Case 1. Preoperative and postoperative 3D CT scan reconstructions. A: Preoperative image demonstrating left coronal synostosis with associated ipsilateral vertical dystopia (harlequin sign), nasal deviation to contralateral side, and compensatory overgrow of the right frontal area. B: Postoperative image, obtained 6 years after surgery, showing correction of the vertical dystopia and realignment of the orbits along the horizontal plane. Also noted is the correction of the deviation of the nasal bones. There is a small persistent area of nonossification on the left frontal area near the coronal osteotomy site. C: Overhead image obtained at 6 years revealing overall normalization of the calvarial vault shape with symmetry of the frontal, parietal, and occipital areas.
therapy (with bitemporal parietal pressure) was instituted for about 10 months. The forehead deformities corrected by 9 months (Fig. 8 right). Marked expansion of the anterior cranial vault was achieved during the 1st postoperative year as were correction of antimongoloid orbital slant and forehead protrusion (Fig. 9). At last report, the child was developing normally with no clinical or developmental delays.

**Discussion**

Multiple-suture synostosis that presents early in infancy and soon after birth poses a great challenge to the treating craniofacial surgical team. The rapidly growing brain, which doubles in volume in the first 9 months and triples by age 2 years, leads to rapidly developing deformities involving the calvarial, orbital facial, and skull base skeleton. The very invasive nature of the conventional calvarial vault remodeling techniques used in most craniofacial centers requires that these patients be treated at later stages (at 6–12 months of age).14–17,19,21 Such delay allows these deformities to worsen, which in turn requires more extensive procedures that are associated with greater risk to the patient. Due to the global involvement of the skull, centers often recommend 2-stage procedures to individually address the frontal and occipitoparietal deformities during separate procedures. Invariably, such delay in treatment leads to changes in skull base, nasal, and orbital morphology and alignment that cannot be corrected with any type of subsequent surgical procedures. The end result is suboptimal, particularly when more than 2 sutures are involved.

As acknowledged by other authors,18 the treatment of bicoronal craniosynostosis does indeed present a significant challenge, particularly as it pertains to correction of both turricephaly and brachycephaly. It is adamantly argued that the only way to correct these deformities is with whole-vault cranioplasty techniques.20 However, our results indicate that if a patient with bicoronal craniosynostosis is treated early with our described techniques, these extensive surgeries may not be needed and may save the child all of the risks associated with the other procedures.

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**Fig. 6.** Case 1. **Left:** Preoperative midcranial CT scan demonstrating the extensive compressive forces of the brain on the overlying skull. The sulcal-gyral pattern is markedly visible in the calvarial bones. Attempts to elevate those bones are fraught with much difficulties including dural tears, parenchymal damage, and bleeding. **Right:** Computed tomography scan done 2 years after surgery shows complete remodeling of the outer and inner skull tables without the need for craniotomies, plates, or screws. Note symmetry of the frontal and parietal bones.

**Fig. 7.** Case 2. **A:** Preoperative photograph of 2-month-old girl with metopic and right coronal craniosynostosis. Vertical dystopia and orbital misalignment, nasal deviation and craniofacial scoliosis are the result of the craniosynostosis. **B:** Photograph taken 8 months after surgery, demonstrating orbital realignment and correction of vertical dystopia as well as nasal deviation correction. The patient underwent linear craniotomies of the coronal and metopic sutures. **C:** At a 3 year follow-up, the patient continues to exhibit normal orbital alignment as well as a straight nose and sagittal alignment of the craniofacial skeleton.

**Fig. 8.** Case 3. **Left:** Ten-week-old boy with bicoronal craniosynostosis. In addition to brachycephaly, the patient has marked forehead protrusion (in front of the tip of the nose) and frontal turricephaly. **Right:** Nine months following endoscopic craniectomies, resection of coronal sutures, and helmet molding therapy. Of major significance is the fact that the frontal turricephaly and frontal bossing corrected without the need for bifrontal craniotomies or orbital bandeau advancement.
Our original goal in approaching these patients with minimally invasive endoscopic techniques at a very early age was simply to halt the progression of associated craniofacial deformities. Our results, however, have demonstrated that not only were we able to halt progression, but were able to significantly reverse many, if not all, of these deformities. As such, this has become our primary mode of treating such cases. We have been careful not to include syndromic cases, as they are associated with many other peculiar and idiosyncratic problems. There have been no deaths and only minimal deficits. The lack of need for blood transfusions is a major advance and advantage.

Lastly, the use of endoscopy-assisted techniques has contributed to a paradigm shift in treatment by allowing us to operate in very young patients. We believe that craniosynostosis leads to inappropriate restriction of brain growth and associated craniofacial deformities. By releasing the stenosed sutures early, appropriate and adequate brain growth takes place, which in turn leads to cephalic normalization as such. Following early suture release, we institute corrective helmet therapy, which constitutes the centerpiece of our postoperative treatment. However, early suture release could not be safely done without endoscopic assistance, lest one risk significant blood losses in these very young infants.

Conclusions

Presented in this report is our experience using minimally invasive endoscopic techniques to treat patients with nonsyndromic multiple suture synostosis. At the very least, these should be considered when diagnosing these patients early in infancy and to halt progressive deformities. However, our results indicate that these techniques alone can lead to major and significant improvement and resolution of presenting signs. They are additionally associated with significantly less morbidity than traditional procedures. Thus, in carefully selected patients, with multiple nonsyndromic craniosynostosis, the early treatment with these techniques ought to be considered as a safe, viable, and successful alternative by the treating surgeon.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

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Address correspondence to: David F. Jimenez, M.D., Department of Neurosurgery, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, MC 7843, San Antonio, Texas. email: jimenezd3@uthscsa.edu.