Age as a critical factor in the success of surgical correction of craniosynostosis

John Persing, M.D., William Babler, Ph.D., H. Richard Winn, M.D., John Jane, M.D., and George Rodeheaver, Ph.D.

Departments of Neurosurgery and Plastic and Maxillofacial Surgery, University of Virginia Medical Center, Charlottesville, Virginia

The effect of timing of the surgical release of prematurely immobilized coronal sutures was studied in rabbits. At 9 days of age, the coronal suture was mechanically immobilized by the application of methyl cyanoacrylate adhesive. These animals and a control group then received metallic implants on each side of the suture to monitor growth. At 30, 60, or 90 days after suture immobilization, separate groups of animals underwent a linear suturectomy to release the restriction. In animals in which the suture was not released, growth at the coronal suture was significantly restricted and resulted in severe deformities in the neurocranium. The benefits derived from surgical release were time-dependent. Suturectomy at 30 days of age resulted within 60 days in achievement of 100% of the growth in sham-treated controls. In contrast, delayed surgery at 60 or 90 days of age resulted in achievement of only 38% and 17% of normal growth, respectively. Angular measurements of the vault and base of the cranium showed a similar graded response toward normality, with the greatest correction occurring with the earliest operation. These results support the clinical impression that early surgical correction of craniosynostosis results in superior cosmetic appearance. A further implication of this work is that abnormality at a single suture strongly influences the development of other areas in the craniofacial complex.

Key Words • craniosynostosis • skull growth • craniofacial abnormality

Most neurosurgeons now believe that surgical correction of craniosynostosis during the neonatal period yields superior cosmetic results. However, experimental studies to support this opinion are lacking. Persson, et al., have demonstrated that early coronal suture fixation can be achieved experimentally in 9-day-old rabbits. This experimentally created restriction of growth at the coronal suture resulted in significant changes of the angular relationships of the cranial vault and base and of the linear dimensions of the cranial base. These findings are consistent with those observed in humans. Moreover, in this rabbit model, surgical release of the immobilized suture at 30 days of age resulted in a return of the cranial vault and base to a "normal" angular relationship. However, as in the clinical condition, the effect of altering the time of the surgical release was not evaluated.

The present study was designed to examine the effects of early (at 30 days of age), intermediate (at 60 days of age), and late (at 90 days of age) surgical release of experimentally induced coronal suture fixation on subsequent cranial base and vault bone growth.

Materials and Methods

Synopsis of Experiment

Thirty-one neonatal rabbits were separated into five experimental groups (Fig. 1). In four of the groups, the coronal suture was physically immobilized. The fifth group of animals was sham-treated. At different time intervals after suture immobilization, three of the experimental groups underwent surgical release of the immobilized coronal suture. The effect of premature coronal suture immobilization and its subsequent release on skull morphology was studied by cephalometric analysis and compared to sham-treated animals.

Experimental Animals

Shortly after birth, litters of New Zealand white (Oryctolagus cuniculus) rabbits were limited to seven
to reduce growth variations resulting from litter size. All animals were maintained on a 12-hour light-dark cycle at 23 ± 1°C with a relative humidity of approximately 40%. Stock diet and water were provided ad libitum.

Model for Craniosynostosis

As described previously, rabbits at 9 days of age were anesthetized with an intraperitoneal injection of sodium pentobarbital (20 mg/kg). Supplemental analgesia was provided by a subcutaneous injection of 1% xylocaine at the vertex of the skull. A midline scalp incision was made to expose the underlying periosteum and coronal suture. The periosteum adjacent to the coronal suture was resected bilaterally, avoiding the sagittal suture, and small holes were drilled into the left frontal and parietal bones. These holes were filled with a radiopaque dental amalgam which served as craniometric markers. A methyl cyanoacrylate adhesive was then placed over the previously roughened surfaces of the frontal and parietal bone of 25 animals, forming a bridge over the coronal suture. When the adhesive solidified, the skin incision was closed with interrupted 5-0 monofilament nylon sutures. These animals served as the immobilized suture group. The same procedure, excluding application of the cyanoacrylate adhesive, was performed on six sham-treated animals.

Experimental Cranietomy

At 30, 60, and 90 days of age, specified subgroups of animals with immobilized coronal sutures were anesthetized with intravenous sodium pentobarbital (20 mg/kg). After a subcutaneous scalp injection of 1% xylocaine, the underlying skull was exposed by a midline incision. A diamond-edged wheel attached to a dental drill was used to perform a linear craniectomy 5 to 7 mm wide that included the coronal suture. The craniectomy was bilateral and extended to each squamosal suture. Special care was taken not to disrupt the underlying dural tissues. Following the craniectomy procedure, the skin incision was closed as described above.

Evaluation of Suture Growth and Skull Morphology

Lateral radiographs of the skulls of sham-treated and immobilized animals were taken at 9, 30, 60, 90, 120, and 150 days of age. For animals that underwent a linear cranietomy, the lateral radiographs were taken at the same time intervals but discontinued 60 days after surgery. Expansion at the coronal suture was determined from the cephalograms by measuring the distance between the metallic implants. The roentgenocephalometric technique described previously was used to minimize error due to growth. With the aid of a Vernier caliper, the measurements were made to the nearest 0.1 mm.

Changes in skull shape were found by measuring seven angular relationships between the cranial vault, base, and face. Using selected craniometric landmarks, the angles were measured by a protractor to the nearest 0.5°. These landmarks were identified on each cephalogram according to the following definitions (Fig. 2):

1. Basion (B) = a point marking the greatest convexity of the anterior border of the foramen magnum
2. Lambda (L) = a point marking the junction of the paired parietal and interparietal bones
3. Anterior marker (Ma) = the most anterior point on the implanted marker in the frontal bone
4. Posterior marker (Mp) = the most posterior point on the implanted marker in the parietal bone
5. Nasion (N) = the most anterior, interior point in the junction of the frontal and paired nasal bones
6. Optic foramen (O) = a point marking the center of the optic foramen
7. Occipital point (Oi) = the deepest point on the outer contour of the occipital bone between the foramen magnum and the external occipital protuberans
8. Rhinion (Rh) = a point marking the most anterior point of the paired nasal bones
9. Synchronosis point (S) = the deepest point on the cartilaginous sphenoid-occipital synchondrosis.

The following reference lines were used:
1. Line BO' = the extension of a line passing through points B and O
2. Line PL = a line tangential to the inferior surface of the anterior palate bone.

The points and lines given above made up the following angles:

1. Basilar-maxillary angle (BO'/PL) = angular relationship of the basicranium and anterior palate bone read at the intersection of lines BO' and PL
2. Basilar-rhinal angle (BO'/RhN) = the angular relationship of basicranium and upper face read at the intersection of lines BO' and RhN
3. Basilar-nasion angle (BO'/NO) = the angular relationship between the anterior cranial base and posterior cranial base read at the intersection of lines BO' and NO
Basilar-anterior marker angle (BO'/MaO) = angular relationship between the cranial base and the anterior vault read at the intersection of lines BO' and MaO
Basilar-posterior marker angle (BO'/MpS) = the angular relationship between the posterior cranial base and middle cranial vault as measured at the intersection of lines BO' and MpS
Basilar-lambda angle (BO'/LS) = the angular relationship of the posterior cranial base to the posterior cranial vault as measured at the intersection of lines BO' and LS
Basilar-foraminal angle (BO'/BOi) = the angular slope of the cranial base relative to the plane of the foramen magnum as read at the intersection of lines BO' and BOi.

Statistical Analysis
The means and standard errors of the changes in distance between markers and changes in angular relationships were computed for each group of animals at the specified time intervals. Student's t-test was used to test for independence between the sham-treated and various experimental groups.

Results
Growth at the Coronal Suture
During the period of 9 to 150 days of age, the markers in the sham-treated animals separated a mean distance of 8.3 mm (Table 1). The greatest degree of separation occurred early, with 50% of the expansion taking place by 30 days of age (Fig. 3). In contrast, animals with a continuously immobilized suture had a mean total expansion of only 0.8 mm, with the majority of the expansion having occurred by Day 30.
Surgical release of immobilized coronal sutures at 30 days of age resulted in a significantly accelerated
expansion of the bone margins which achieved 100% of the sham-treated growth value by 60 days after surgery. In contrast, delaying surgical intervention until 90 days of age resulted in little compensatory growth. Suture expansion in this case had achieved only 17% of the value of sham-treated animals at 150 days of age. An intermediate compensation of 38% of normal was attained by surgical release at 60 days of age.

The immediate separation of the markers, resulting from surgical release, was determined from radiographs taken preoperatively and compared to those taken immediately after surgery. Regardless of the time of surgical intervention, the immediate expansion at the site of the removed suture was never larger than 0.3 mm.

Changes in Angular Dimension

Immobilization of the coronal suture caused a significant alteration in craniofacial configuration. Following immobilization, there was an immediate and significant alteration in every cranial angle evaluated (Fig. 4 and Table 2). Only when the craniectomy was performed early did sufficient compensatory growth occur to ameliorate all of the angular deformations. In contrast, a late craniectomy at 90 days of age had no effect on the cranial morphology. In this group of animals, the angular relationships remained the same as in animals not undergoing the craniectomy. At the intermediate time of 60 days of age, craniectomy resulted in a moderate return to a “normal” configuration. During this intermediate growth period, the facial complex is still developing and may compensate for the earlier inhibition. However, the angles associated with the vault did not have the same magnitude of compensation, and these angles remained significantly different from those in the control animals.

Discussion

The success of surgical correction of craniosynostosis is dependent not only on identifying the anatomical anomalies, but also on the timing of the intervention. Our previous study\(^9\) described an animal model which generated craniofacial anomalies with the specific anatomic anomaly resulting from a prematurely immobilized coronal suture. Using this model, we quantitatively documented the influence of timing on the results of surgery.

Application of methyl cyanoacrylate adhesive to the coronal sutures of young rabbits resulted in a rapid and significant cessation of normal skull growth. In agreement with Virchow’s hypothesis,\(^7\) the growth perpendicular to the coronal suture was primarily affected. Lack of growth at the coronal suture resulted in a brachycephalic skull with characteristic anterior-posterior shortening.

In control animals, the growth at the coronal suture was very rapid, and 51% of the 9- to 150-day expansion occurred between 9 and 30 days of age. An additional 28% occurred between 30 and 60 days of age, with the remaining periods accounting for 12%, 6%, and 4%, respectively. Bone growth can be directly related to the expanding brain mass, which undergoes approximately the same percentage of increase during these time periods.\(^4\)

This early growth phase appears to be critical for the success of surgical release of the immobilized coronal suture. When the surgical release was performed at 30 days, there was an accelerated compensatory growth phase which returned the skull to a “normal” shape within 60 days. During this early period, the skull is still developing, and has the potential for compensatory remodeling. However, when surgery was delayed, this potential to remodel was lost. Surgery at 60 days resulted in limited compensatory growth and remodeling. An even poorer growth compensation was obtained when the surgery was delayed until 90 days of age.

Compensatory growth expansion at the released coronal suture was correlated with alterations in the spatial relationships of the craniofacial components. The most significant angular alterations occurred following surgery at 30 days of age. With early sur-
Age factor in craniosynostosis surgery

### TABLE 2
Comparison of differences in angular dimensions at the conclusion of the observation period between suture-immobilized and sham-treated animals

<table>
<thead>
<tr>
<th>Angle</th>
<th>No Craniectomy</th>
<th>Craniectomy at 90 Days</th>
<th>Craniectomy at 60 Days</th>
<th>Craniectomy at 30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ</td>
<td>p</td>
<td>Δ</td>
<td>p</td>
</tr>
<tr>
<td>BO'/PL</td>
<td>4.0</td>
<td>0.025</td>
<td>4.0</td>
<td>0.025</td>
</tr>
<tr>
<td>BO'/RhN</td>
<td>4.2</td>
<td>0.005</td>
<td>6.2</td>
<td>0.050</td>
</tr>
<tr>
<td>BO'/NO</td>
<td>4.6</td>
<td>0.025</td>
<td>4.6</td>
<td>0.025</td>
</tr>
<tr>
<td>BO'/MaO</td>
<td>11.0</td>
<td>&lt; 0.001</td>
<td>8.7</td>
<td>0.005</td>
</tr>
<tr>
<td>BO'/MpS</td>
<td>4.6</td>
<td>0.025</td>
<td>4.3</td>
<td>0.025</td>
</tr>
<tr>
<td>BO'/LS</td>
<td>4.8</td>
<td>0.010</td>
<td>5.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BO'/BOi</td>
<td>5.2</td>
<td>0.005</td>
<td>8.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*For definitions of angles, see text. Δ = mean difference in the total angular change for the observation period compared to sham-treated animals for the same time period. p values = significance according to Student's t-test. NS = not statistically different (p > 0.05).

Surgery, all of the angles shifted toward sham-treated values and became similar to the control animals within 60 days. These angular changes were consistent with a rapidly expanding coronal suture which allowed the cranial base to rotate downward, and the facial complex to move forward and down.

Some spatial reorientation also occurred when surgical release was performed at 60 days of age. At this time interval, the facial complex is still developing, whereas the cranial vault has reached its adult shape. Thus, the potential for compensation was realized only for the anterior angles BO'/PL, BO'/RhN, and BO'/NO, which reflects the relationship of basi-cranium to the midface. Because of compensatory alterations, these angles become similar to those of control animals by 120 days of age. The angles associated with the vault had less potential for alteration and remained significantly different from control animals.

Surgical release of an immobilized coronal suture on a 90-day-old rabbit did not result in compensatory alteration of the skull morphology. At this age, the growth potential necessary for compensation has been exhausted.

The results of the present study give experimental documentation to the clinical belief that surgical correction of craniosynostosis should be initiated at a young age. Delaying the surgery until the patient is older has often been recommended, to decrease the morbidity and mortality associated with this extensive and prolonged surgical procedure. However, significant technical advances, especially in the area of anesthesia, have greatly reduced the risk of surgery in infants. Moreover, in their assessment of need to correct

![Fig. 4](image-url) Alteration in cranial morphology for the various experimental groups is depicted. The data plotted are the mean changes in the specific angles during each time interval. White circles = sham-treated at Day 9; black squares = suture immobilized at Day 9; white squares = craniectomized at Days 30, 60, or 90 following immobilization at Day 9.

the prematurely fused cranial suture, neurosurgeons may not have appreciated the associated vault and facial abnormalities that will rapidly develop. Therefore, in view of the results obtained in this study showing limited achievement of normal growth with delayed surgery, surgical correction of craniosynostosis should ideally be performed at the earliest possible age.

Furthermore, this study has implications with regard to the pathogenesis of craniosynostosis and craniofacial anomalies. The well known theory proposed by Moss postulates an abnormality in the base of the skull with consequent vault deformity. Our studies have shown that the reverse is possible. Perhaps, combined cranial and facial anomalies, such as Crouzon's syndrome, can be created by more than one mechanism. Our clinical impression is that some, but not all, cases of Crouzon's disease will show amelioration of the midface deformity if the skull is treated radically and early. Perhaps in those cases, the leading abnormality was in the skull. On the other hand, early and radical reconstruction of the skull and brow can be unsuccessful with early recurrence of the deformity. In these cases, the base of the cranium may be more important.

References


This study was supported by NIH Grant 5-T32-DE-07037.

Dr. Persing was awarded the Donald D. Matson Award for Pediatric Neurosurgery for his contribution to this work. Dr. Winn is a recipient of a Research Teacher Investigator Award from the NINCDS, Grant K07 NS004404 01.

The preliminary results of this study were presented at the Annual Meeting of the American Association of Neurological Surgeons, April 20–24, 1980, at New York, New York.

Address reprint requests to: George T. Rodeheaver, Ph.D., Department of Plastic Surgery, Box 332, University of Virginia Medical Center, Charlottesville, Virginia 22908.