Intracranial Volume Post Cranial Expansion Surgery Using Three-Dimensional Computed Tomography Scan Imaging in Children With Craniosynostosis

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Background: Craniosynostosis is a congenital defect that causes ≥1 suture to fuse prematurely. Cranial expansion surgery which consists of cranial vault reshaping with or without fronto-orbital advancement (FOA) is done to correct the skull to a more normal shape of the head as well as to increase the intracranial volume (ICV). Therefore, it is important to evaluate the changes of ICV after the surgery and the effect of surgery both clinically and radiologically.

Objective: The aim of this study is to evaluate the ICV in primary craniosynostosis patients after the cranial vault reshaping with or without FOA and to compare between syndromic and nonsyndromic synostosis group, to determine factors that associated with significant changes in the ICV postoperative, and to evaluate the resolution of copper beaten sign and improvement in neurodevelopmental delay after the surgery.

Methods: This is a prospective observational study of all primary craniosynostosis patients who underwent operation cranial vault reshaping with or without FOA in Hospital Kuala Lumpur from January 2017 until Jun 2018. The ICV preoperative and postoperative was measured using the 3D computed tomography (CT) imaging and analyzed. The demographic data, clinical and radiological findings were identified and analyzed.

Results: A total of 14 cases (6 males and 8 females) with 28 3D CT scans were identified. The mean age of patients was 23 months. Seven patients were having syndromic synostosis (4 Crouzon syndromes and 3 Apert syndromes) and 7 nonsyndromic synostosis. The mean preoperative ICV was 880 mL (range, 641–1234 mL), whereas the mean postoperative ICV was 1081 mL (range, 811–1385 mL). The difference was 201 mL which was statistically significant ($P < 0.001$). In comparison, the mean volume increment for syndromic synostosis and nonsyndromic synostosis was 282 mL and 120 mL, respectively. The difference was statistically significant ($P < 0.004$). Three months post-operation, the copper beaten sign was still present in the CT scan which was statistically not significant in this study ($P > 1.0$). However, there was 100% (n = 13) improvement of this copper beaten sign. However, the neurodevelopmental delay showed no improvement which was statistically not significant ($P > 1.0$).

Conclusion: Surgery in craniosynostosis patient increases the ICV besides it improves the shape of the head. From this study, the syndromic synostosis had better increment of ICV compared to nonsyndromic synostosis.

Key Words: 3D CT scan, children, Cranial vault reshaping, Craniosynostosis, Fronto-orbital advancement, Intracranial volume

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Primary craniosynostosis is a congenital malformation owing to fusion of ≥ sutures during embryogenesis. It occurs in 1 in 2100 to 1 in 2500 births and it can be either nonsyndromic or syndromic.[1] During the first year of life, the brain triples in volume and continues to grow rapidly for the next 2 years and reaching adult size between 6 and 10 years of age. The cranial sutures are essential to growing skull to accommodate the brain growth.[2] The cranial sutures consist of metopic sutures, separating the paired frontal bone; sagittal sutures, separating the paired parietal bone; coronal sutures, separates the paired frontal and parietal bone; and lambdoid sutures, separating parietal and occipital bone.

The cranial abnormality will result in abnormal shape of the skull, depending on the suture that was involved. This insufficient skull growth will result in raised intracranial pressure (ICP). Elevation in ICP (defines as ≥15 mmHg during slow-wave sleep) was more common in syndromic cases compared to single suture synsotosis which is reported in around 14%.[3] The risk of elevation of ICP depends on the number of affected sutures in the nonsyndromic type. Meanwhile, in syndromic patients it is related to multifactorial cause which includes intracranial venous obstruction, hydrocephalus, and upper airway obstruction.[4]

The classic presentations of elevated ICP are headache, nausea, and vomiting. The consequence of delayed in diagnosis of this elevated ICP may cause neurodevelopmental delay in children. Mild impairment in cognitive and motor function has been seen in patient with single suture synostosis. It was reported around 30% to 35% of school-age children with single suture synostosis have neurocognitive impairment.[5,6] But in group of syndromic patient, neurodevelopmental delay was worse as a moderate delay in mental and motor scores was reported.[7]

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A computed tomography (CT) scanning and three- dimensional (3D) reconstruction has become the standard preoperative diagnostic in craniosynostosis.[8] Typical primary radiological findings included ridging, sclerosis, or narrowing of the sutures.[9,10] Secondary signs are fingerprinting or copper beaten sign, which may indicate raised ICP.[10] A diffuse copper beaten sign was seen more commonly in craniosynostosis patient and it is correlated with elevation of ICP. However, it is not recommended as screening tool because of low sensitivity.[11]

The surgical correction consists of cranial vault expansion and FOA.[12] Most of surgery was performed between ages 6 months and 2 years.[1] The aims of surgical treatment are to increase the intracranial volume (ICV), thus reducing the risk of developing elevated ICP, and to correct the skull abnormality. However, there is still debate about relationship between ICV and symptoms of raised ICP and the effect of surgery on ICV.

Therefore, this is a volumetric study using 3D CT scan to measure ICV changes in children with craniosynostosis after the surgery. From this study, we hope to see the effect of surgery on improvement of copper beaten sign and neurodevelopmental delay.

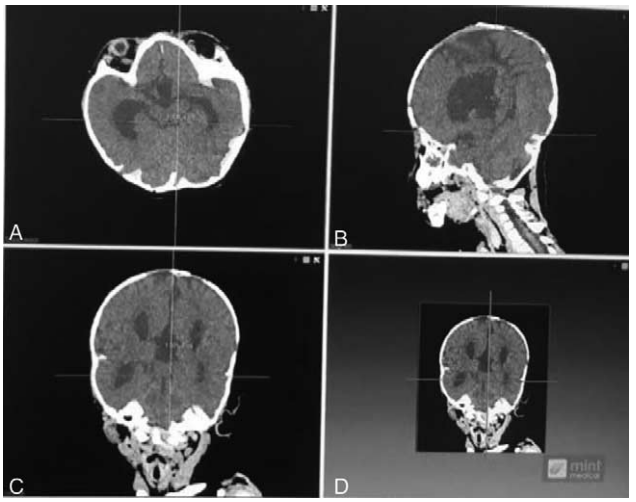

FIGURE 1. Multiplanar view of delineation of the ICV.

METHODS

Research Design

An observational prospective study was conducted on 14 patients who had primary craniosynostosis and underwent operation cranial vault reshaping with or without fronto-orbital advancement (FOA) in Hospital Kuala Lumpur from January 2017 to June 2018. Approval to undertake the study was obtained from the Research and Ethics committee KKM (NMRR 34174). The sample size was calculated based on paired *t* test analysis. A sample size of 15 patients required to detect 290 mL changes of ICV preoperative and postoperative at power 80% and 0.05 significant level with 10% dropout.

Study population

The inclusion criteria were all cases in pediatric age group up to 12 years' old, and all types of craniosynostosis either non-syndromic or syndromic involving single sutures or more. The surgery was done in Hospital Kuala Lumpur with preoperative CTB 3D done within 2 months before surgery and patients followed up for at least $\geq$3 months. The CTB 3D was repeated 3 months after operation and all CTB 3D were readable in Digital Imaging Communications in Medicine (DICOM). Meanwhile, the exclusion criteria were patients who had secondary craniosynostosis, and patients who underwent re-surgery. Patients who were lost to follow-up and the CTB 3D without soft copy were also excluded.

Methods of Research

3D CT Scan

We retrieved the 3D CT brain data of the studied subject from the database of HKL Radiology department with the permission of the head of unit. All 3D CT brain were performed in 4 mm slices before and after surgery. The 3D CT images were transferred in Picture archiving and communication system (PACS) gateway, and organized in DICOM format. The selected data that were retrieved from PACS were saved in compact disc (DVD-R).

Volumetric Study

For measurement of ICV in this study, 2 observers (author and co-author) measured the volume preoperatively and postoperatively. The ICV of each set was compared to see the inter-rater agreement between 2 observers. The ICV was calculated using the Medical Imaging Interaction Toolkit (MITK) open source software which is used for visualization, semiautomatic segmentation, and volumetric analysis. MITK is an open software (C++) under a BS-style license, developed by the German Cancer Research Centre and recognized by the Open Source Initiative (OSI) public benefit corporation. It was validated by Fritzsche et al.[13] Measurements were carried out on a Dell Precision T7500 Workstation with an Intel Xeon CPU E5606 @ 2.13 GHz and 24 GB RAM. The ICV was performed by semiautomatic segmentation by selecting on region of interest (ROI) on axial plane followed by region growing method. This region growing method was started in a chosen pixel, a seed point and manually traced by means of computer mouse-driven pointer to accept or reject the neighboring pixel. Manual trace was based on exact delineation of structures to achieve border of ROI. The ROI is defined in each slide of CT brain from axial view. A visual assessment then followed on coronal and sagittal views, determining the contour of ROI to improve accuracy of segmentation (Fig. 1). After satisfactory segmentation results, the software automatically generated and displayed a volume in millimeters cubic (mL).

Delineation of ICV

For determination of ICV, the bone–brain interface was identified, as bone appears white (high density) and the brain appears gray (medium density). The ROI was determined in axial view just above foramen magnum until just beneath the vertex of skull.

Imaging Characteristic

CT imaging was reviewed by blinded radiologist to determine the sutures affected, presence of copper beaten sign preoperative, and the resolution of copper beaten sign 3 months postoperatively.

Clinical review

With the Denver developmental chart, patients were screened for the developmental delay preoperatively and were reassessed for any improvement 3 months postoperatively.

Statistical Analysis

Data entry and descriptive analysis were performed using SPSS program for windows version 22 (SPSS Inc, Chicago, IL). The demography was expressed in the table forms using the mean and standard deviation (SD) for numerical variables and numbers and percentages for categorical variables. To study the difference in ICV pre-and postoperatively, paired *t* test was used and independent *t* test was used to compare the difference in increment of ICV in syndromic synostosis and nonsyndromic synostosis. Analysis of

variance was used to determine factors associated with significant changes in ICV. To determine the resolution of copper beaten sign and improvement of neurodevelopmental delay post-operation, Mc Nemar test was used. The statistical significance was considered when $P < 0.05$. To measure the inter-rater agreement between 2 observers, the intraclass correlation coefficient (ICC)was used. The value ICC > 0.8 was considered as excellent correlation.

RESULTS

Data from 14 patients who underwent anterior cranial vault reshaping with or without FOA between January 2017 and Jun 2018 were collected. The demographic data of the patients were analyzed. All 28 3D CTB—14 preoperatively and 14 post-operatively—were obtained and measured. The difference of these volumetric data was calculated.

Demographic

The age of craniosynostosis patients who underwent surgery ranged from 11 months to 6.9 years with the mean age 23 months. The group consisted of 6 males and 8 females. They were equally divided into syndromic synostosis (4 Crouzon syndrome and 3 Apert syndrome) and nonsyndromic synostosis patients. Clinically, none of these patient have any symptom of increase in ICP (worsening headache in the morning, vomiting or seizure), but majority of them presented or referred to our center because of abnormal shape of the head except 2 patients who were referred because of eye abnormality (exophthalmos). Radiological sutures that were involved were bilateral coronal in 5 patients, sagittal in 4 patients, unilateral coronal in 2 patients and multiple sutures in 3 patients. None of them were associated with hydrocephalus or tonsilar herniation.

Volume

The mean preoperative ICV was 880 mL (standard deviation [SD], 195 mL), and mean 3-month postoperative ICV was 1081 mL (SD 221). The difference between mean preoperative and postoperative ICV was 201 mL, an increase of 22%. This difference was statistically significant ($P < 0.001$) (see Table S1, Supplemental Digital Content, http://links.lww.com/SCS/A774)

From this study, there was no association between age and type of suture affected with the volume changes postoperative. All these factors were not statistically significant (see Table S2,S3, Supplemental Digital Content, http://links.lww.com/SCS/A774)

In this study, we compared the mean volume changes between syndromic synostosis and nonsyndromic synostosis. The mean volume increment for syndromic synostosis was 282 mL (SD 216 mL), an increase of 36%. Whereas in the non-syndromic synostosis the mean volume increment was 120 mL (SD 50 mL), an increase of 13%. This difference between both type of craniosynstosis after the surgery was statistically significant ($P < 0.004$) (see Table S4, Supplemental Digital Content, http://links.lww.com/SCS/A774)

Patients with syndromic sysnostosis (n = 7) had preoperative mean volume 871 mL (SD 217 mL) and postoperative mean volume 1153 mL (SD 230 mL). The preoperative and postoperative mean volumes in non-syndomic synostosis were 889 mL (SD 187 mL) and 1010 mL (SD 202 mL), respectively.

The volumetric data were analyzed for ICC, which show no significant difference between 2 observers. The ICC was 0.9 which is excellence correlation between 2 observers.

Resolution of Copper Beaten Sign Post-operation

Of 14 patients, only 1 patient did not have copper beaten sign before surgery. After 3months of surgery, all 13 patients still have the copper beaten sign which is statistically not significant ($P > 1.0$) (see Table S5, Supplemental Digital Content, http://links.lww.com/SCS/A774). We categorized the degree of resolution of copper beaten sign as 1) no improvement, 2) incomplete resolution (Figs. 2A, 2B) and 3) complete resolution (Figs. 2C, 2D). From this category, all 13 patients had incomplete resolution which showed us radiological improvement post-surgery.

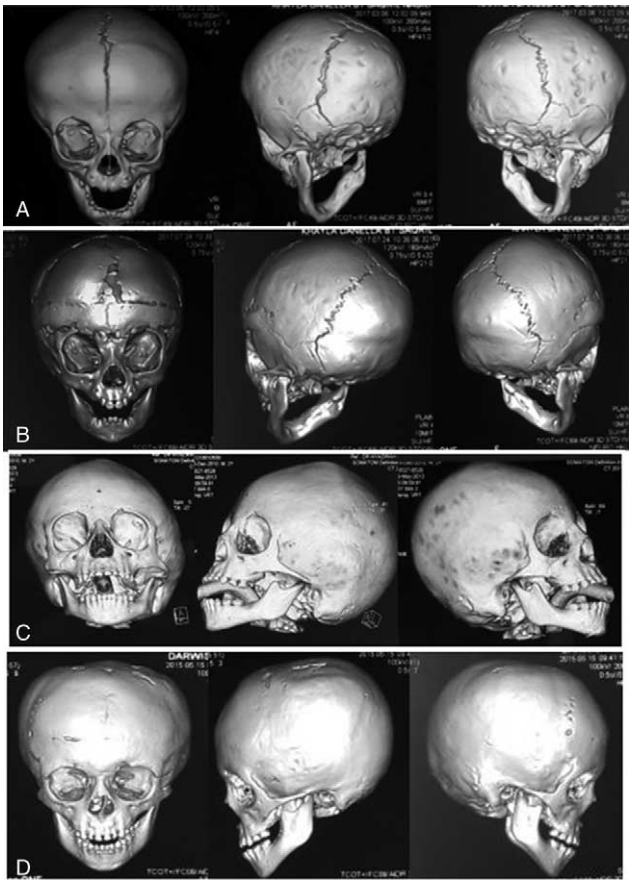

FIGURE 2. (A) 3D CT imaging preoperative showed significant of copper beaten sign. (B) 3D CT imaging showed incomplete resolution of copper beaten sign 3 months post-surgery. (C) 3D CT imaging preoperative showed significant of copper beaten sign, (D) 3D CT imaging showed complete resolution of copper beaten sign 3 years post-surgery.

Improvement in Developmental Delay

Only 2 patients had developmental delay and both of them were syndromic patients. One of them had global developmental delay, whereas the other had speech delay. Both of them did not show any improvement after 3 months of operation which is statistically not significant ($P > 1.0$) (see Table S6, Supplemental Digital Content, http://links.lww.com/SCS/A774).

DISCUSSION

Craniosynostosis is associated with higher risk of increased ICP. The aim of surgery is to increase the ICV, so that it could prevent the neurologic sequel of increased ICP. In our study, we found that the growth curve of ICV in sagittal and unilateral synostosis was almost similar to normal children, which was comparable with study done by Kamochi et al.[14] However, in syndromic patient (Apert and Crouzon) and bilateral coronal synostosis the ICV was below

normal. This finding was differ from Kamochi et al[14] as they reported the ICV was normal in Crouzon and bilateral coronal synostosis and above normal in Apert syndrome.

We compared our study with the ICV growth curve by Kamochi et al[14] because so far, in our knowledge, there was no study of ICV done using Malaysian children population. This ICV growth curve was more geographically comparable to our study because of the Asian population children. However, the small difference in our finding compared to this study could be because of small number of our patients.

In this study, we focused on ICV changes in craniosynostosis patients who underwent cranial expansion surgery (see Table S7, Supplemental Digital Content, http://links.lww.com/SCS/A774). Patients with sagittal suture synostosis underwent anterior cranial vault reshaping. Meanwhile, other single suture synostosis (bilateral coronal, unilateral coronal) and all syndromic patients had anterior cranial vault reshaping with FOA. We found that the ICV changes were 201 mL, an increase of 22% at 3 months post-surgery. The syndromic synostosis had increment of 282 mL, 36% increase of ICV compared to nonsyndromic patients which was 120 mL, 13% increase of ICV. Although the preoperative ICV of syndromic patient was 889 mL, not much difference compared to nonsyndromic patient which was 871 mL, this significant increment of ICV in syndromic patient could be because of FOA procedure in addition to anterior cranial vault reshaping. As we know, syndromic synostosis usually associated with midface hypoplasia and their orbital roof was shallow resulting in ocular proptosis. This FOA procedure was done to correct the abnormal orbital roof and to restore the normal shape of orbital rim in relation to the eye.

In our study, the percentage of ICV changes for nonsyndromic patients was lower compared to study done by Clement et al.[15] They reported mean ICV increase was 191.5 mL (28%) within average of 101 days. For syndromic synostosis, Posnick et al[16] reported the ICV gain varied from 34 to 608 mL in Crouzon syndrome. Meanwhile, for Apert syndrome, the ICV gain varied from 82 to 1155 mL. This was comparable to our study wherein Apert syndrome had more ICV changes between 151 and 661 mL compared to Crouzon syndrome where the ICV changes were from 117 to 197 mL.

Copper beaten sign referred to the prominent convolution markings which were seen mostly in the inner table of the skull. It was thought to be related to the raised ICP. These markings were featured by depression corresponding to gyri of the brain and the thicker intervening bony ridges corresponding to cerebral sulky. This copper beaten sign was seen more commonly in craniosynostosis patient and it was associated with elevated ICP as reported by Tuite et al.[11] However, it was reported by van der Meulen et al[17] that these convolution markings might be normal during period of rapid brain growth. In our study, 92% (n =13) of patients had copper beaten sign preoperatively, but all of them had no symptoms of increased ICP (headache, vomiting, irritability). We found that there was no correlation between the copper beaten sign and the clinical symptom of raised ICP in the patients, although it was demonstrated by Agrawal et al,[18] patients with copper beaten appearance were symptomatic up to 45%. We can conclude that copper beaten sign was not an effective screening to evaluate patient who had raised ICP in cranisynostosis patient and this was supported by Tuite et al[11] because of low sensitivity.

After 3 months of operation, although the copper beaten sign was still present, we could see 100% (n = 13) improvement in resolution of copper beaten sign in our study. This could be because of increase of ICV which provides more space to allow normal expansion of brain. Thus, it will prevent the continuous pulsatile pressure from the growing brain on the cranium that causes the copper beaten sign earlier. Here, we can see the complete resolution of copper beaten sign after 3 years operation, a case from our center that was not included in our present study (Figure 2C and D). However, these findings were different from the study done by Guimarães-Ferreira et al[12] wherein they reported a significant increase in the copper beaten appearance post-surgery. Their possibility of this increase of copper beaten appearance was because of spatially irregular bone resorption and deposition related to the extensive devascularization and homogenous revascularization of large bone flaps.

In our study, there was no association with the hydrocephalus in craniosynsotosis patient. However, it was reported by Cinalli et al[19] about 8.1% patients from 1727 cases had hydrocephalus and was found to be more common in syndromic patients. This different finding is most probably because we conduct a small group of patients in our study.

In craniosynostosis patients, various studies showed there was association with the neurodevelopmental delay. Two main factors that contribute to this were elevated ICP with hypovascularity and secondary cerebral deformation resulting from brain growth owing to abnormal shaped of the skull. It was reported by Kapp-Simon et al[20] around 35% to 40% of patients with single suture synostosis had behavioral or cognitive abnormality such as learning disability and language impairment, although the global development was within normal range. This suggested that single suture synostosis had risk for cognitive or motor deficit or learning/language disabilities as high as 3- to 5-fold. This was supported by Starr et al[21] and Bellew et al[22] who demonstrated significant neurodevelopmental deficit in single suture synostosis when compared to control group. However, Bellew et al[22] reported improvement of neurodevelopmental delay after the surgery.

In our study, we found that only 14% (n = 2) of our patients had neurodevelopmental delay and both cases are of syndromic synostosis (Apert syndrome). But, 3 months post operation, both cases showed no improvement. In study done by Starr et al,[21] they reported developmental delay that persists after the surgery which was similar to our findings. In their study, patient was assessed postoperatively at 18 months of age. The possibility of their findings was because of the differences after the operation which were not very sensitive to be detected in infant. Other factor was there may be refractory period after surgery (recovery period) that causes infant perform worse during post-surgery assessment. However, in our study, this negative finding could be because of short duration of assessment following surgery which was 3 months. Our findings were also similar to the study done by Abbas Nejad et al,[7] which demonstrated syndromic patient had significant developmental delay compared to nonsyndromic patient. However, surgery did not impact neurodevelopment outcome of the syndromic group, but was reported to be effective in nonsyndromic group.

CONCLUSION

From our study, there was significant increase in the ICV after the cranial expansion surgery in children with craniosynostosis. It allows normal brain growth and development by giving space to the brain after the surgery. This will prevent the neurological sequel from raised ICP including neurodevelopmental delay. Here, we could see the syndromic synostosis patient had better increment in ICV compared to nonsyndromic patient, which could be because of FOA procedure in addition to cranial vault reshaping. Although there was no statistical change in radiological and clinical outcome, possibly limited by small sample size and short duration of study, we strongly believe that these changes in ICV would correlate with some degree of improvement in copper beaten sign and neurodevelopmental delay in long term study in the future.

Limitation and Future Recommendations

As with other studies, this study also has some limitations. This study is a prospective observational study, but it has small number of patients because of limited time frame as candidates need to complete the analysis early. Apart from that, the duration of this study is not enough for us to see more changes in radiological and clinical outcome of patient. To improve this study, retrospective observational study can be done to overcome the small sample size in the future. We suggest this study to be followed up further up to 3 years to see long-term outcome from clinical and radiological perspectives.

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