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Research article

Investigating mechanical properties for developing a human infant cranial bone surrogate in pediatric craniofacial surgery

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A R T I C L E I N F O

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A B S T R A C T

Beyond the surgeon's feedback on bone behavior in the operating room, there is a paucity of data present in the literature on the mechanical properties of pediatric calvarial bone. The present study tested the calvarial bone of four species (Adult Humans, Dog, Pig, and Monkey) to find the mechanical properties. Three types of tests were performed; flexural, compression, and torsion to mimic how bone is handled during the surgery and the results were further compared with the existing published data for human pediatric calvarium. Test results indicated a significant difference between the modulus ($p = 0.006$ for flexural, 0.0002 for compression, and 0.0075 for shear) and strength ($p = 0.0005$ for flexural, 0.0051 for compression, and $p < 0.0001$ for shear) amongst the tested groups. Compared with published data, the flexural properties of the 12-day-old pig were found to be closest to that of an 11-month-old human infant ($E = 0.783$ GPa). In contrast, the adult human was found to have a flexural modulus 3.9 times that of the pig, and specimen thickness of adult humans had a strong positive correlation ($r = 0.77$, $p = 0.0237$) with its flexural modulus, strengthening the disparity between infant and adult human skull bone material properties. Based on these results, neonatal piglet calvarium was selected as a model for 1-year-old human infants commonly presented for total cranial vault reconstruction. These results will help to inform the development and use of new technologies and techniques for bone graft manipulation in the laboratory and the operating room.

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1. Introduction

An essential component of performing total cranial vault remodeling surgery to treat craniosynostosis is reshaping the infant's calvarium bone to achieve the desired geometric shape and form, and thus functional and aesthetic outcomes. Such tasks can be challenging due to the unique characteristics of the infant skull. The human adult cranial bone, analogous to engineering sandwich structures, is comprised of a lightweight and spongy core in the middle referred to as the diploë, surrounded by an inner and outer table made up of stiff cortical bone [1]. The diploë is organically soft and thickens as the human ages, which leads to higher values of mechanical properties such as bending strength [2]. Unlike an adult's skull, the infant's skull can substantially deform in response to an external force. This is due to the presence of thin, pliable bony tissue that has partly calcified, and the outer table is relatively thinner, providing flexibility for rapid brain growth as the bone develops throughout childhood [3].

However, the mechanical characteristics of the newborn calvaria are not well documented because of the restrictions on the availability of infant cadavers [4]. Surgeons possess some knowledge of physical properties due to their tactile usage and manipulation of calvarium bone in the operating room (OR) during craniosynostosis surgery [5]. Still, it may not be enough to characterize the basic mechanical behavior of bone, as surgeons are continuously looking for new ways to manipulate the bone.

Previous studies have looked closely at the mechanical properties of infant and adult human skulls relevant to the biomechanics of obstetric fetal head molding (low loading rate) or head injuries during accidental and inflicted impacts (high loading rate). McElhaney et al. [6] and Wood [7] were among the first to examine adult bone samples collected from the complete calvarium in the context of cranial traumas, while McPherson and Kriewall [8] employed the fetal cranial bone to comprehend the biomechanics of fetal head molding. Following these studies, Margulies and Thibault [9] extracted mechanical properties from infant cranial samples at both low and high rates, and Coats and Margulies [10] further investigated pediatric trauma by testing both bone and sutures at high rates. Most recent studies have further investigated the mechanical properties of the human calvarium through dynamic and quasi-static testing. Zwirner et al. ([11] characterized the high strain rate (2.5 m/s and higher) bending behavior of human bone using a custom-built drop tower where the sample age ranged from 3 weeks to 94 years. Adanty et al. [12] performed four-point bending tests on adult frontal and parietal bone samples to determine morphometric, geometrical, and mechanical properties.

However, loading rates are directly proportional to the mechanical parameters [10]. Neither the obstetric nor the neurotrauma (which involve brain and spinal cord) scenarios can be reliably extrapolated to provide insights into the bone's response to manual manipulation in the OR, in which the bone endures a moderate loading rate. Therefore, further mechanical testing is required to better understand and delineate the limits of deformational change for the infant bone during craniosynostosis surgery.

To circumvent the shortage and size limitations of newborn calvarium bone for mechanical testing, a representative animal model or adult bone can be used. In the context of neurotrauma, the biomechanical properties of neonatal piglet calvarium have been shown to correlate well with human infant calvarium, but this correlation is highly dependent on the day of life at euthanasia, which increases the cost and logistical difficulty of using the piglet model [13]. As such, we sought to explore and add alternative species from readily available animal tissues at our institution.

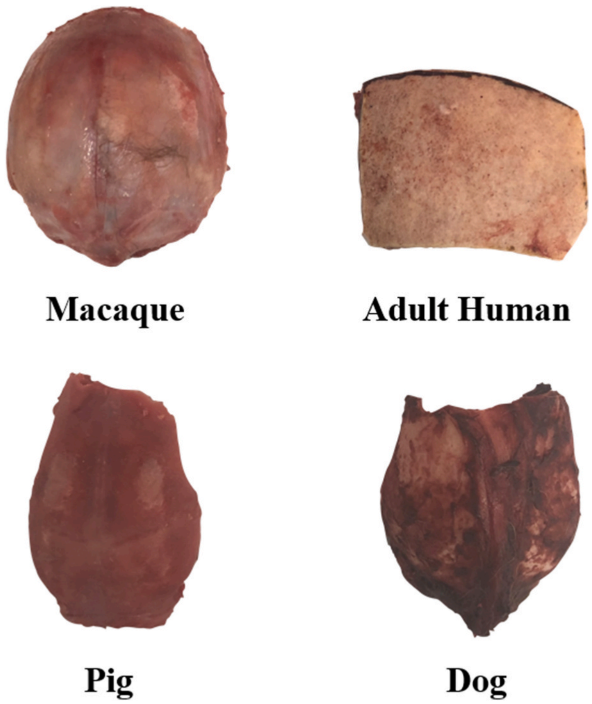

Fig. 1. Top view of the calvarium bone of species tested in the study.

This study aims to find the mechanical properties of the calvarial bone of four species under American Society for Testing and Materials (ASTM) standard testing conditions to further compare the results with published data for the human pediatric calvarium. We hypothesize that among the tested animal species, there exists at least one species whose calvarial bone's mechanical properties align closely with those observed in the human infant calvarium bone. Factors such as bone thickness and age will also be considered to determine the optimal cadaver bone. This alignment of mechanical properties will indicate the potential suitability of the chosen species as an alternative model for studying bone deformation during surgical procedures and shape manipulation. The chosen model will be used in further studies on the bone's mechanical response to osteotomy patterns and controlled bone weakening such as that performed in the OR, to develop new techniques to improve our ability to affect bony deformation.

2. Methods

2.1. Cranial bone acquisition

Animal calvaria samples were obtained through the University of Illinois' Animal Care Committee (ACC) tissue-sharing program. Our institution's readily available species included Cynomolgus/Rhesus monkey and Beagle canine. Age-specific pig calvaria was unavailable through the institution's tissue-sharing program and was obtained through a regional research animal supplier (Yorkshire/Landrace/Duroc white farm pig). Adult human calvaria samples were obtained through the Anatomical Gift Association of Illinois (AGAI). Fig. 1 shows the calvarial bone of the four tested species where, except for adult humans (obtained as bone segments from the parietal region), the whole calvaria of macaque, pig, and dog can be seen. The study utilized fresh bone samples that were frozen upon arrival and stored at - 40 °C until further processing.

2.2. Sample preparation

Before harvesting the specific specimen size needed for testing, bone samples were thawed at room temperature (~25 °C). Specimens were extracted from the cranial vault in a specific orientation (anterior to posterior) using a MicroLux® Variable Speed Multi-Saw (Micro-Mark, NJ, USA) with a 0.40 mm thick precision saw blade. Only parietal bone was extracted from each subject, in an orientation parallel to and on either side of the sagittal suture to achieve consistent relative values amongst tests while avoiding any bone-suture-bone samples.

2.3. Study design

Three types of mechanical tests were performed: flexural/bending, compression, and torsion to mimic the action of bending, flattening, and twisting of bone by the surgeons using bending forceps in the OR during craniosynostosis surgery. Testing speeds were adjusted to approximate the rate of manual bone deformation as determined by visual analysis of intraoperative video footage (Fig. 2). For each mechanical test, the sample size was calculated based on power analysis with an effect size of 1.6, alpha error and power of 0.05 and 0.8 respectively [9]. A total sample size of 8 specimens each was calculated using G*Power 3.1.9.7 statistical software (G*Power, Düsseldorf, Germany). Groups consisted of Adult Humans (mean age = 75 ± 7.97 years, 4 Male: 74.75 ± 5.18; 4 Female: 75.75 ± 10.99), Macaque monkeys (mean age = 4.5 ± 0.92 years, 5 Male: 4.8 ± 1.09; 3 Female: 4 ± 0), Beagle dogs (mean age = 2.2 + 0.37 years, 8 Males and 0 Female), and Yorkshire/Landrace/Duroc pigs (mean age = 12 days, 4 Male: 12 ± 0; 4 Female: 12 ± 0). The flexural and compression tests were performed using an MTS 30/G universal testing machine (UTM) (MTS Systems, MN, USA). In contrast, the torsion test was facilitated by a combination of custom-fabricated experimental hardware. The load-displacement curve obtained from the tests was subjected to further analysis to extract parameters to find the mechanical properties of calvarium bone. A

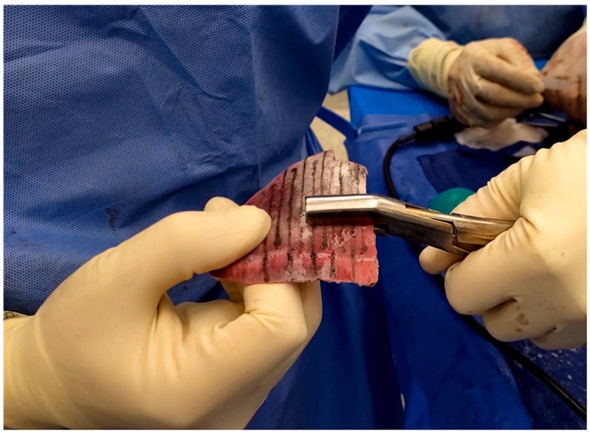

Fig. 2. Surgeon using free hand bending forceps to bend the bone during craniosynostosis case.

workflow comprising the major steps of the study is shown in Fig. 3.

2.4. Mechanical testing

2.4.1. Three-point bend (3 PB)/Flexural test

Specimens were tested in a three-point bend testing setup (Fig. 4) using an ASTM-certified Model 642.10B bend fixture (MTS Systems, MN, USA) rated with a maximum force capacity of 100 kN. The UTM was equipped with a 150 kN rated load cell (MTS Systems, MN, USA), capable of a high data acquisition rate for smaller displacements. A support span of 25 mm was kept to adhere to the recommended span length to thickness ratio based on ASTM standard test D790 [14]. Specimen dimensions were 30 mm long, 20 mm wide, and 2–3 mm thick, except for the average thickness of adult human specimens (7.24 mm). The test ran at a loading rate of 10 mm/min and all the specimens were tested until fracture. Force and centerline deflection were recorded and a load-displacement curve was generated by the test software TestSuite TW (MTS Systems, MN, USA). The modulus of elasticity or flexural modulus was calculated using the stress-strain curve, and ultimate flexural strength was regarded as the stress at the peak point of this plot. The bone specimens can be assumed to behave as homogenous, flat Euler-Bernoulli beams. The elastic modulus (E) can be calculated using the Bernoulli-Euler equation. This involves further calculating flexural stress (σ) and strain (ε) using equations (1) and (2) to validate the flexural modulus:

$$\sigma = \frac{3FS}{2WT} \tag{1}$$

$$\varepsilon = \frac{6\delta T}{S} \tag{2}$$

where F is the peak load/force at the point of failure, S is the span length, W and T are the width and thickness of the specimen respectively and δ is the crosshead displacement from the start of the test to the end.

2.4.2. Compression test

The compression test was performed based on the ASTM D695 [15] by using the ASTM-certified 643 compression platens Model

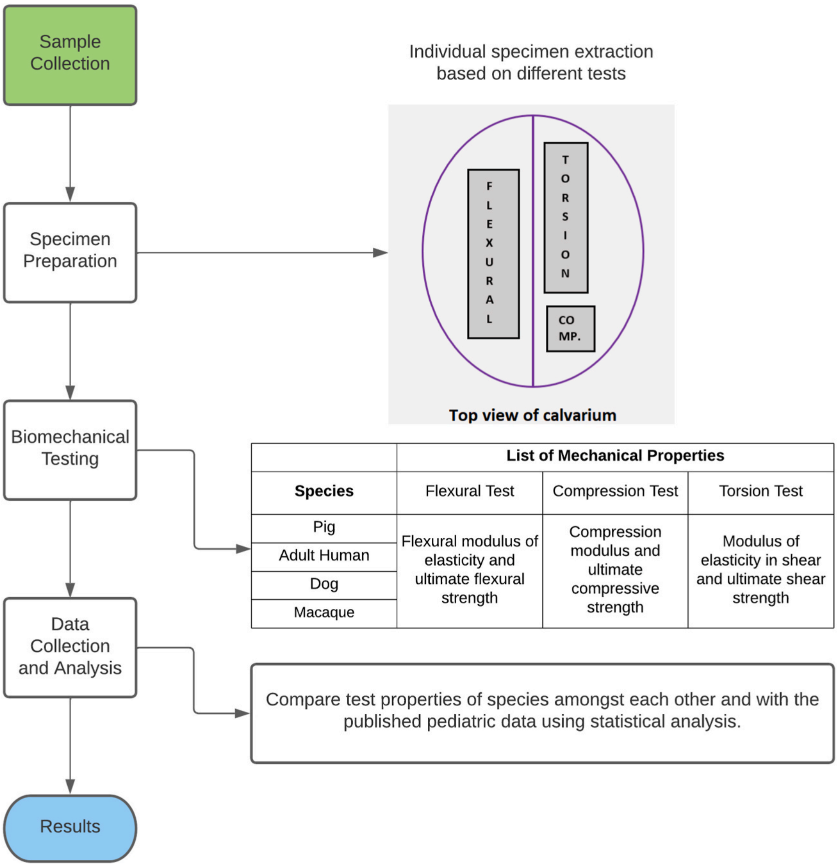

Fig. 3. Workflow diagram of the study.

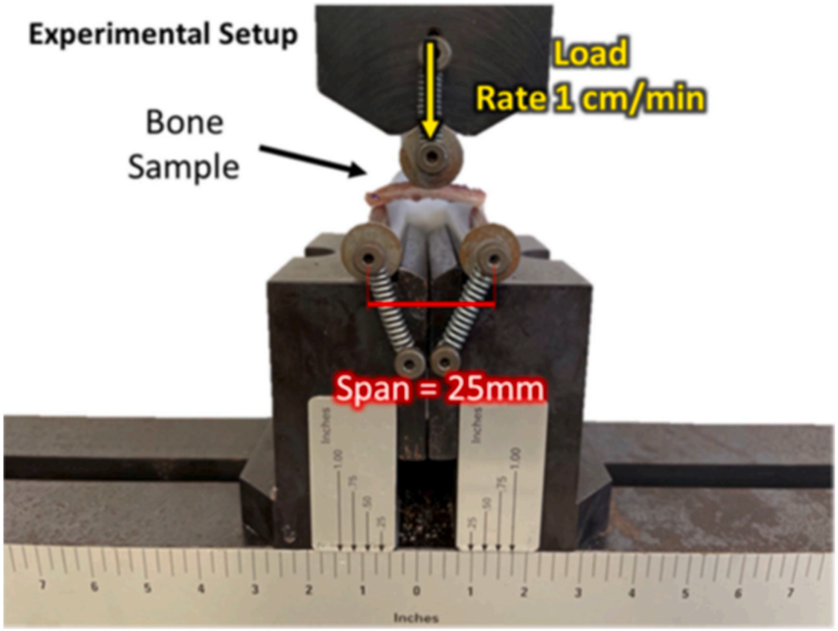

Fig. 4. Experimental setup for flexural/three-point bend test of bone samples.

643.15A-03 (MTS Systems, MN, USA) [Fig. 5(a)]. The platens were used to apply even pressure on the test specimens which were 5 × 5 mm square-shaped discs of 2–3 mm thickness except for adult human specimens, which on average had a thickness of 7.69 mm ranging from 3.8 to 10.5 mm. A pre-load of 10N was applied to secure the specimen and any sharp edges (if they existed) can be smoothed to minimize any chances of inertial load being used at the start of the test and ensure a maximum ideal stress field and state during testing [16]. The test was stopped after 10 % of the specimen's original height was compressed, and the test software generated a load-displacement graph. The stress at the maximum point of the stress-strain plot curve was defined as the ultimate compressive strength (σ), while the compressive strain (ε) was the fractional decrease in length of the test specimen due to compressive stress. Both of these parameters were provided by the test software but were also calculated using equations (3) and (4) to validate:

$$\sigma = \frac{F}{A} \tag{3}$$

$$\varepsilon = \frac{\Delta L}{L} \tag{4}$$

Where F is the load/force, A is the original minimum cross-sectional area of the test specimen, ΔL is the change in thickness of the

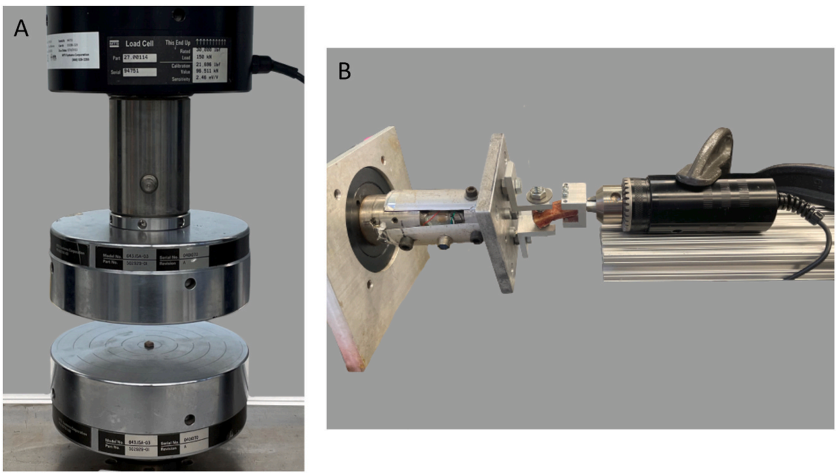

Fig. 5. Experimental setup for (a) compression test and (b) torsion test of bone samples.

specimen, and L is the original thickness of the specimen.

2.4.3. Torsion test

Customized test hardware consisting of T-slot aluminum frames (80/20, IN, USA), Arduino Uno R3 microcontroller board (Arduino, MA, USA), Nema 17 Stepper Motor (OMC Corporation Limited, Nanjing City, China), Torque Gauge Model MTT03-100 (Mark-10, NY, USA), 3-D printed and CNC machined bone holding fixtures were used to perform the torsion test to mimic the action of bending and twisting of bone by the surgeons in the OR using bending forceps. However, to achieve a fracture point with more rigid adult human bone, a Kollmorgen Goldline XT Servo Motor Model MTC306B1-E2C1 (Kollmorgen Corporation, VA, USA) was deployed to complete the testing while keeping the rest of the setup unchanged as shown in Fig. 5(b). Specimen dimensions were 35 mm × 20 mm × 2–3 mm thick except thickness for adult human specimens (7.85 mm). The test ran at an angular speed of 2°/sec and was programmed to stop when the motor completed a rotation of 90°, even though the specimens fractured sooner than that. The torque gauge recorded the torque experienced by the specimen at failure, and subsequent readings were recorded by MESUR® Lite data collection software (Mark-10, NY, USA). Equations (5) and (6) show formulas used to calculate ultimate shear strength ($\tau_{\max}$) and modulus of elasticity in shear (G) [17,18]:

$$\tau_{\max} = \frac{T}{c_1 ab^2} \tag{5}$$

$$G = \frac{TL}{c_2 ab^3 \varphi} \tag{6}$$

Where T is torque applied to the specimen, L is the length of the specimen, φ is the angle of twist, c_1 and c_2 are coefficients depending on the a/b ratio, where a and b are the wider and narrower side of the cross-section, which in our case is the width and thickness of the specimen respectively.

2.4.4. Statistical analysis

To determine differences in the means of the mechanical test parameters across the four species, a one-way analysis of variance (ANOVA) with post hoc analysis was utilized. Linear regression was further used to assess the nature of the relationship and correlation coefficient (Pearson) between the mechanical properties and factors such as specimen thickness and sample age. While comparison between species was the primary goal, the linear regressions helped characterize relationships within each group to better understand the consistency of the comparative data. The statistical significance level was set as $p < 0.05$ for all the reported analyses.

3. Results

Three-point bending results comparing the flexural modulus and ultimate flexural strength showcased statistically significant differences among the means of four tested species ($p = 0.006$ for modulus and 0.0005 for strength). Compression testing results showed a significant difference between the compression modulus ($p = 0.0002$) and strength ($p = 0.0051$) between the tested groups and so did the torsion test results ($p = 0.0075$ for shear modulus and $p < 0.0001$ for strength). A complete summary of the calculated mechanical properties is tabulated in supplemental Table 1.

Following confirmation of the means of two or more species being different, the mean flexural modulus was found to be 3440.75 MPa (SD 2002.50 MPa, 95 % CI [1767, 5115] MPa) for an adult human, dog (Mean 1930.54 MPa, SD 1276.11 MPa, 95 % CI [863.7, 2997] MPa) and macaque (Mean 1720.79 MPa, SD 1158.51 MPa, 95 % CI [752.3, 2689] MPa). However, there was a statistically significant difference observed between pig's parietal bone flexural modulus (Mean 880.27 MPa, SD 358.11 MPa, 95 % CI [580, 1180] MPa) in comparison with adult humans ($p = 0.0034$). Also, the difference in pig's mean ultimate flexural strength (28.85 MPa, SD 7.98 MPa, 95 % CI [22.19, 35.53] MPa) when compared to adult humans (61.06 MPa, SD 13.77 MPa, 95 % CI [49.54, 72.58] MPa) was considered statistically significant ($p = 0.0175$) along with two other comparisons between pig and dog (Mean 69.05 MPa, SD 22.51 MPa, 95 % CI [50.23, 87.87] MPa, $p = 0.0024$) as well as pig and macaque (Mean 74.43 MPa, SD 29.58 MPa, 95 % CI [49.70, 99.17] MPa, $p = 0.0006$).

The differences in mean compressive modulus for adult humans (2791.43 MPa, SD 1169.14 MPa, 95 % CI [1814, 3769] MPa), dog (Mean 2257.28 MPa, SD 1187.75 MPa, $p = 0.68$, 95 % CI [1264, 3250] MPa), and macaque (Mean 2811.86 MPa, SD 919.07 MPa, 95 % CI [2044, 3580] MPa, $p > 0.99$) were not statistically significant. However, the mean compressive modulus of adult humans was considered highly statistically significant from pig (Mean 582.26 MPa, SD 231.75 MPa, 95 % CI [388.9, 776.4] MPa, $p = 0.0004$). Furthermore, compressive modulus comparisons between pig and dog ($p = 0.0082$), as well as pig and macaque ($p = 0.0004$) also showed significant differences. The mean compressive strength for the adult human calvarium was 15.44 MPa (SD 13.52 MPa, 95 % CI [4.141, 26.75] MPa), dog (Mean 7.88 MPa, SD 2.55 MPa, 95 % CI [5.745, 10.02] MPa), and macaque (Mean 13.82 MPa, SD 5.73 MPa, 95 % CI [9.024, 18.62] MPa). The difference in pig's parietal bone compressive strength (2.12 MPa, SD 0.78 MPa, 95 % CI [1.470, 2.787] MPa) was considered highly statistically significant in comparison with adult humans ($p = 0.0068$) and macaque ($p = 0.0199$).

Similarly, in the torsion test, the mean modulus of elasticity in shear and ultimate shear strength for adult human's parietal bone was found to be 628.54 MPa (SD 211.42 MPa, 95 % CI [451.8, 805.3] MPa) and 44.99 MPa (SD 9.56 MPa, 95 % CI [37.0, 52.99] MPa) respectively. While comparing with dog's modulus of elasticity in shear (Mean 494.56 MPa, SD 173.77 MPa, 95 % CI [349.3, 639.8] MPa) and macaque's (Mean 496.61 MPa, SD 148.46 MPa, 95 % CI [372.5, 620.7] MPa), and ultimate shear strength for dog (Mean

42.68 MPa, SD 14.23 MPa, 95 % CI [30.78, 54.58] MPa) and macaque (Mean 38.55 MPa, SD 5.61 MPa, 95 % CI [33.86, 43.25] MPa), the differences were considered to be not statistically significant. In comparison to adult humans, pig's parietal bone had a modulus of elasticity in shear (Mean 308.27 MPa, SD 130.32 MPa, 95 % CI [199.3, 417.2] MPa, $p = 0.0038$) and ultimate shear strength (Mean 17.60 MPa, SD 6.14 MPa, 95 % CI [12.46, 22.74] MPa, $p < 0.0001$), and their differences in means were statistically significant. Lastly, pig's ultimate shear strength showcased significant differences when compared with dog ($p < 0.0001$) and macaque ($p < 0.0008$). Graphical results of statistical analysis for all the bone specimens with calculated mechanical properties are presented in Fig. 6(a and b).

With crack propagation being consistent between species, some variability within samples likely stemmed from biological differences and microstructural inhomogeneity. The bone samples in three-point bending exhibited cracks initiating on the surface within the middle region of the span length. The cracks propagated fully across the width perpendicular to the loading direction for these species. In contrast, samples tested in torsion showed cracks originating closer to the loading point and propagating at an angle across the width.

Despite the limited variation in the sample impacting statistical power, a linear regression was performed to explore the correlations. None of the mechanical properties of adult humans and macaques had a strong association with age. Interestingly for the dog, its flexural modulus and age suggested a very significant, and strong correlation between the two values ($p = 0.0003$, $r = 0.94$) as shown in [Fig. 7(a)]. Similarly, the thickness of the individual specimen from all the species was analyzed for its association with the mechanical test parameters. As shown in [Fig. 7(b)], a strong positive correlation was found between the flexural modulus of adult humans and bone thickness ($p = 0.0237$, $r = 0.77$). No trend of correlation was found in the remaining species.

4. Discussion

This study offers essential data on the material properties of a potential surrogate for infant human cranial bone. Currently, no literature exists that investigates the material properties of multiple species at the rates employed by surgeons during craniosynostosis

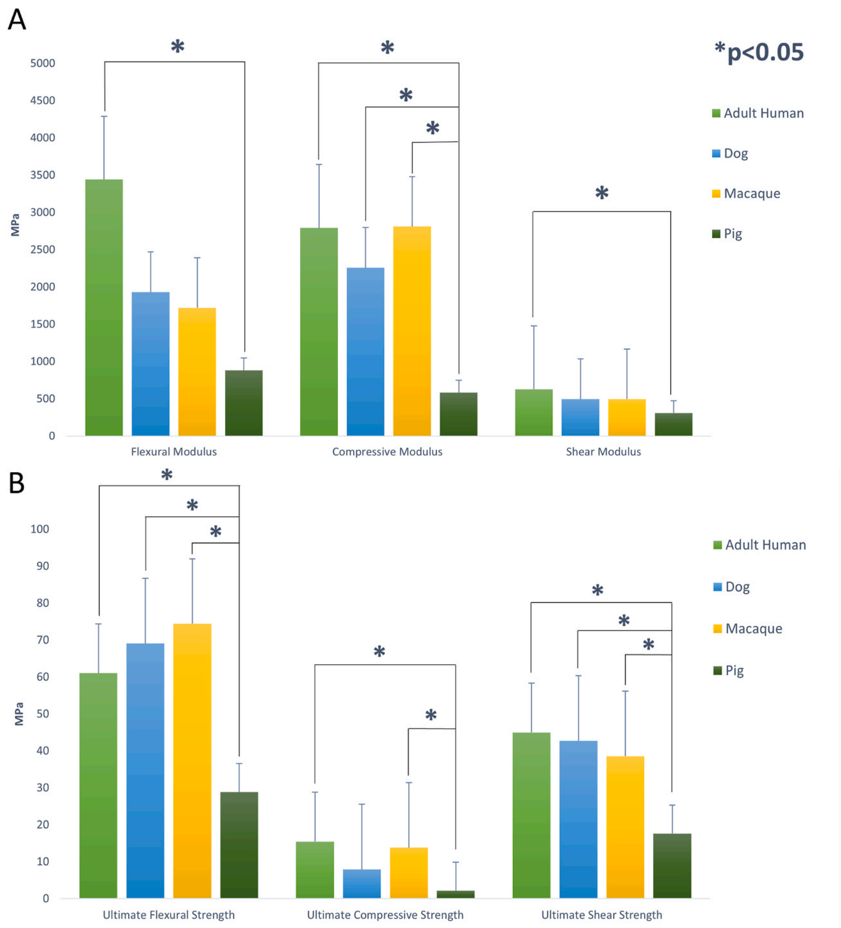

Fig. 6. Mean values of mechanical test properties (a) modulus and (b) strength of all the species with error bars represent standard error. Significant differences were found between Adult humans and Pig across all the test parameters (* indicates significant differences, $p < 0.05$).

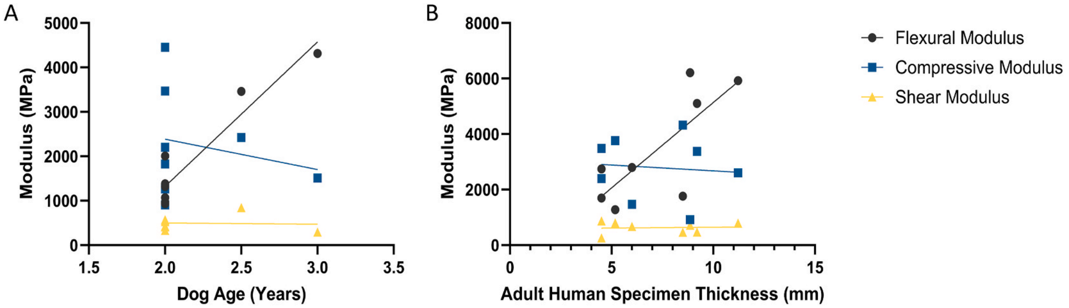

Fig. 7. (a) Correlation of all dog's modulus when compared to the age of the specimen in years and (b) all adult human's modulus when compared to the thickness of the specimen.

surgery. A previously published study by Baumer et al. [13] was conducted to compare infant pig cranial bone and its suture with human pediatric patients, intended to offer data on the relationship of age between the two species at high loading rates. In terms of flexural stiffness, the study found a correlation between the days of pig age and the months of human age. Up to 14 days of pig age, there was no discernible variation in properties, but after that, they were observed to deviate from human data. This led to the inclusion of the neonatal pig animal model in this current study. Furthermore, Margulies and Thibault [9] conducted a three-point bending test on pig and newborn cranial bone and discovered similarities in parameters such as elastic and rupture modulus, as well as the energy absorbed to failure.

The results of this study show that the neonatal pig animal model (Mean 880.27 MPa, SD 358.11 MPa, 95 % CI [580, 1180] MPa) has flexural/bending properties closest to that of an 11-month-old human infant ($E = 783.8$ MPa) and falls close to the reported values at both slow and fast loading rates [9,10] (Fig. 8(a) and b). In contrast, the adult human was found to have a flexural modulus 3.9 times that of the pig. According to Margulies and Thibault [9], the elastic modulus of human cranial bone at the time of birth tested in three-point bending is reported to range from $\leq$1000 MPa (quasi-static) to 1371.4 MPa (dynamic), but is not comparable to the adult values. Recently Igo et al. [19] reported the elastic moduli of adult bone to be roughly 3 times more than pediatric cranial bone (subjects ranging from 4 to 10 months) in four-point bending. However, their mean moduli (4.19 $\pm$ 2.09 GPa) and ultimate stress (92.99 $\pm$ 26.10 MPa) values of pediatric cranial bone were significantly greater than that obtained by Coats and Margulies [10] (Bending modulus: 461.1 $\pm$ 63.8 MPa and ultimate stress: 30.2 $\pm$ 4.8 MPa) and the results of this study for pig species (Bending modulus: 880.27 MPa, SD 358.11 MPa, 95 % CI [580, 1180] MPa) and ultimate stress (28.85 MPa, SD 7.98 MPa, 95 % CI [22.19, 35.53] MPa). These discrepancies may be explained by specimen age and biological variability, both in terms of material composition and structure, other sources of potential disparity include modulus calculation method, the cranial bone sample storage and preparation, or the testing methodology [19].

There was no statistically significant difference between the mean flexural modulus and ultimate flexural strength of macaque and dog compared to adult humans, there was a statistically significant difference for the pig. Although adult bone properties and morphology significantly differ from those of an infant, they enabled us to illustrate relative comparisons between species. The adult data serves as an endpoint in the spectrum toward which pediatric bone develops. Comparing animal models to both adult and published pediatric data aided in determining the model that best aligns in terms of properties.

McElhaney et al. [6] concluded that material properties of adult human and primate cranial bone such as hardness, density, and local compression strength are not significantly different. This is in agreement with our results for both compressive modulus and ultimate compressive strength of adult humans, primates, and dogs. The compressive modulus (2.79 GPa, SD 1.17 GPa, 95 % CI [1.814, 3.769] GPa) and strength (15.44 MPa, SD 13.52 MPa, 95 % CI [4.141, 26.75] MPa) reported in this study for adult parietal bone was

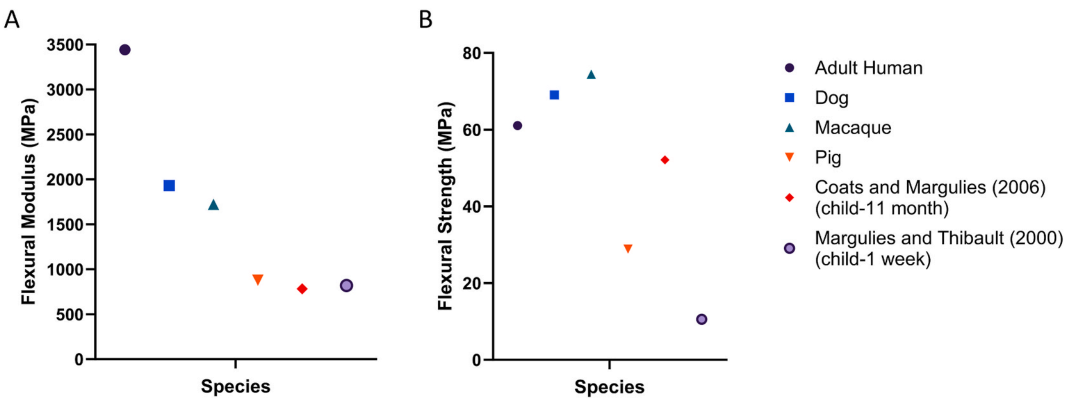

Fig. 8. Comparison of flexural modulus (a) and strength (b) of the studied species with specimens of infant cranial bone from previous literature.

lower than values reported by McElhaney et al. [6] which ranged from 2.41 ± 1.44 GPa - 5.58 ± 3.03 GPa. However, their testing incorporated multiple cranial regions including parietal, occipital and frontal bone in contrast to our study which is reporting values for the parietal bone only. As noted in more recent studies, the frontal bone exhibits greater modulus and ultimate stress values compared to the parietal region [19,20]. By isolating the parietal bone, we likely captured properties on the lower end of McElhaney et al. reported range [6]. Variability in testing methods may also contribute to disparities between studies. While absolute values differ, our key finding of significantly lower pediatric versus adult cranial bone modulus aligns with overall trends in the literature. However, further investigation using standardized testing protocol is needed to elucidate the source of these differences with prior data.

Similarly, the high strain rate dynamic flexural properties characterized by Zwirner et al. [11], incorporating all regions of the adult cranial bone (frontal, temporal, parietal, and occipital), surpassed our flexural test results. This observation is consistent with the expected rate-dependence of bone mechanical properties. The authors calculated bending strength at three different loading rates (2.5 m/s: 98 MPa; 3.0 m/s: 119 MPa; 3.5 m/s: 130 MPa), all of which exceeded our calculated bending strength for adult human calvarium (10 mm/min: 61.06 MPa). More recent studies have further characterized the compressive properties of human calvarial bone using updated testing methods. Alexander et al. [21] performed microstructure based compressive testing on adult bone samples (aged 78, 79, and 86 years) to present results based on distinct regions. They reported a combined compressive modulus of 3.3 ± 1.0 GPa; 2.5 ± 0.7 GPa for the composite parietal bone. Zhai et al. [22] found similar results while conducting compressive testing on calvarial bone samples (ages 70–74 years) using multiple strain-rates ranging from quasi-static (0.01/s) to high (625/s) including intermediate (30/s). They concluded that mechanical properties of human cranial bone increases as the strain rate increase and thus were strain rate sensitive. Both these studies are in agreement with the results presented in our study.

Overall, the compression properties of an adult human, dog, and macaque calvarial bone appear similar, while the pig calvarium stands apart from the other tested species. Torsion testing yielded quite similar results as pig was statistically significantly different in mean modulus of elasticity in shear ($p = 0.0038$) and ultimate shear strength ($p < 0.0001$) when compared with adult humans. The compressive properties for adult humans, as characterized by Adanty et al. [12], were found to be greater than our test results (mean 37.39 MPa vs our study's 15.44 MPa). This difference was anticipated, given the calculation of compressive properties using a four-point bend setup in the former study, as opposed to our study's use of compression platens.

For adult humans, sample age did not significantly affect the mechanical test properties since the average age of the tested adult human specimens was 75 years (range: 65–91 years), well past the maturation age of cranial bone. However, the specimen thickness had a strong positive correlation with the adult human's flexural modulus, which means as the specimen thickness increases, the flexural modulus increases. This is consistent with previous findings in which skull bone thickness and density were discovered to be the primary factors influencing the mechanical properties of skull bone [1,23]. Interestingly, dog's flexural modulus showed an increasing trend with age ($p = 0.0003$, $r = 0.94$).

Fig. 9(a–c) shows specimens that underwent testing along with their location of failure/crack. Crack initiation and propagation patterns between species provided insights into the fracture behavior and mechanisms of the calvarial bone. Cracks forming away from the maximum bending moment region may indicate a more brittle nature and susceptibility to shear stresses compared to the perpendicular cracking corresponding to tensile failure from the dominant bending deformation. Investigation of the microstructure and failure patterns could further help characterize the mechanical limits and properties of the bone.

Based on these results, neonatal piglet calvarium was selected as a model for 1-year-old human infants commonly presented for total cranial vault reconstruction. It should be noted that this conclusion is drawn in comparison to the adult dog and primate calvarium used in this study. And thus future research should include neonatal specimens of other species to confirm the suitability of

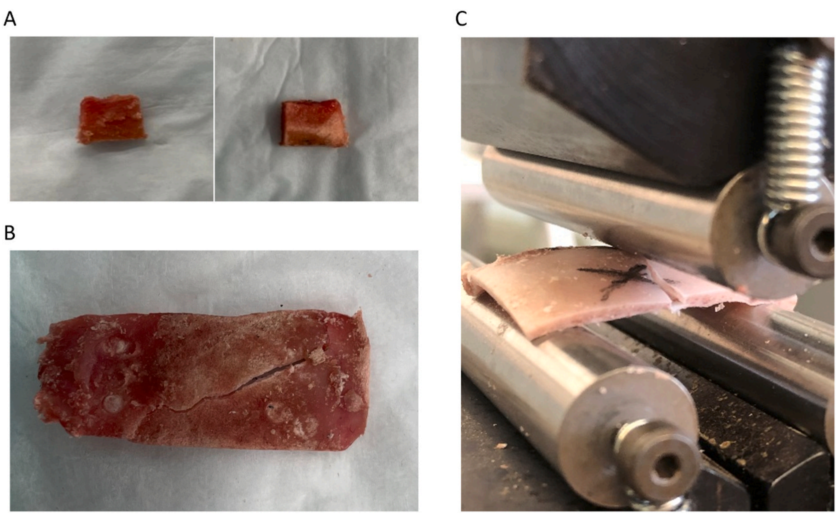

Fig. 9. Before and after compression testing of pig specimen (a), crack propagation in pig specimen during flexural testing (b) and macaque specimen during torsion testing (c).

the piglet model more conclusively. In addition to the current study, future studies will involve controlled testing of the calvaria from different species, evaluating their response to manual handling, manipulability, cutting, drilling, and pliability. The piglet model will be further explored via the finite element analysis (FEA) method using CT data outlined by Alexander et al. [24] and Budiarsa et al. [25] to infer the elastoplastic and the fracture behavior of infant cranial bone [9,26,27]. Knowledge of these properties will provide us insights into the practical limits of bone deformation. This will further help to inform the development and use of new technologies and techniques for bone graft manipulation in the laboratory and the OR [28].

5. Limitations

The study is limited to the comparison of existing infant cranial bone data found in the literature. Conducting experiments with pediatric calvaria using the same apparatus and test settings would have strengthened the study significantly. However, strict legal regulations and ethical concerns regarding the use of pediatric human tissues, coupled with the time-consuming process of obtaining age-specific samples to meet the study's size requirements, led to comparison with existing infant cranial bone data. Also the variation within each sample due to comparatively smaller sample size may affect the statistical power and generalizability of the correlation analyses.

The Euler-Bernoulli beam theory used to calculate flexural properties is only strictly valid for beams with a length significantly greater than the cross-sectional dimensions, whereas the bone samples had a relatively short span length compared to the thickness. This could result in shear stresses influencing the strain calculations. Additionally, the inhomogeneous density and microarchitecture of the bone's internal structure, especially the diploë layer, introduces non-uniform material properties that are not captured by modeling the bone as a homogenous beam. These limitations may lead to inaccuracies in the calculated stress and strain values from the bending test data. However, the equations still provide a useful approximate measure of the flexural properties for comparison between groups. The relative trends observed should still hold relevance, even if the absolute stress/strain magnitudes are affected by the simplifying assumptions.

6. Conclusion

This study was the first to compare multiple species across three biomechanical tests at moderate loading rates. Our findings suggest that the adult cranial bone properties of the human, dog and macaque are farthest from published infant human data and would not be considered potential surrogates for further testing. While the neonatal piglet seems to be the best available animal model, this conclusion is based on the comparison with adult specimens of other species. Future studies should investigate the mechanical properties of neonatal specimens from other species to provide a more comprehensive assessment. However the adult cranial bone of dog and macaque species may find utility in certain situations where the cost of the neonatal piglet model is prohibitive. Hands-on training of medical students and residents in tissue handling and cranioplasty techniques may benefit from the use of readily available, lower-cost animal cadaver bone which handles in a reasonably similar way to human infant bone.

CRediT authorship contribution statement

Devansh Saini: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Roberto Leonardo Diaz:** Writing – review & editing, Software, Methodology, Investigation, Data curation. **Farid Amirouche:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Conceptualization. **Jose L. Cataneo:** Methodology, Investigation, Data curation. **Sydney A. Mathis:** Methodology, Investigation, Data curation. **Mitchell A. Marques:** Methodology, Investigation, Data curation. **Quintin L. Williams:** Jr, Writing – review & editing, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Linping Zhao:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Russell R. Reid:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Lee Alkureishi:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Ethics approval

Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC) approval was not required for adult human, dog and monkey. For adult human, the Office for the Protection of Research Subjects (OPRS) at university of Illinois at Chicago determined that the specific human cadaver bone did not represent human subjects research and, therefore, did not require the submission of a determination application: Projects limited to death records, autopsy records, or cadaver specimens provided that the cadaveric tissues/cells was not used for clinical investigations. For monkey and dog, the tissue were obtained through a tissue sharing program at UIC. The animals were humanely euthanized as part of other studies that were approved by the Animal Care Committee, UIC's institutional animal research oversight committee. The university has a tissue sharing program to reduce animals used in research in accordance with the principles of the three Rs (reduce, replace, refine). Finally, for pig, the study was approved by the Institutional Animal Care and Use Committee (IACUC) on January 25, 2021 under the ethics approval protocol ID: 011221-1. The study complies with all regulations.

Data availability statement

Has data associated with your study been deposited into a publicly available repository? No (Data included in article/supp. material/referenced in article).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Lee Alkureishi reports financial support was provided by Chicago Biomedical Consortium. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

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