DESIGN OF A NOVEL HEAD FIXATION DEVICE FOR MR GUIDED FOCUSED ULTRASOUND BLOOD-BRAIN-BARRIER-OPENING PROCEDURES

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Design of a Novel Head Fixation Device for MR Guided Focused Ultrasound Blood-Brain-Barrier-Opening Procedures

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Abstract

Focused Ultrasound (FUS) is an emerging, non-invasive technology that provides an alternative to the treatment of several neurological disorders such as essential tremor and Glioblastoma Multiforme (GBM). FUS has been shown to disrupt the BBB in a safe and targeted manner, however, head fixation devices used for this procedure were originally designed for radiosurgery. In response, the research team proposed the development of a novel head frame for FUS applications. The creation of the design was accomplished based on the following important overarching objectives: 1) to reduce design bulkiness in order to minimize image distortion, 2) increase the BBBO treatment envelope, and 3) to maximize patient comfort. Design iterations were created using the computer-aided design (CAD) software, Fusion 360, after which the final design was 3D printed and assembled to create a prototype. Finite element analysis (FEA) was conducted on the frame using Fusion 360 to determine the safety factor and the maximum force that can be applied to the rotating swivel screws at the front of the device prior to deformation. Static stress finite element analysis of the novel headframe prototype was tested with an average torque of fixation of 0.348 Nm and a maximum torque of fixation of 0.522 Nm. This demonstrated a maximum force of 273.1 MPa with a safety factor of 1.0, and a maximum force of 409.7 MPa with a safety factor of 0.67, respectively.

Keywords: FUS, BBBO, GBM, stereotactic head frame, FEA

Introduction

In the United States alone, there are about 6 cases of gliomas diagnosed per 100,000 people every year[1]. Gliomas are brain tumors that originate from glial cells and can be characterized by being diffusely infiltrative in nature. Such tumors affect surrounding brain tissue and can be difficult to access, especially in the context of treatment. Glioblastoma multiforme (GBM) is the most aggressive type of glioma and accounts for 45.2% of malignant tumors in the CNS. GBM carries a poor prognosis for patients, with only about 5.5% of those affected surviving five years post-diagnosis[2]. Given the low survival rate associated with GBM, there is a need for more efficacious treatment options. One such treatment that has shown potential to do this is Focused Ultrasound (FUS), which is an early stage, non-invasive technology utilized in the treatment of a multitude of neurological disorders, including gliomas, such as GBM. FUS utilizes a multitude of intersecting beams of ultrasound. At the focal point, the energy created by the convergence of the multiple beams results in a variety of biological effects. A notable treatment of interest that employs FUS technology is the reversible opening of the blood-brain barrier (BBBO) which allows for drug delivery and therapeutic access to brain cells. The blood-brain barrier (BBB) is extremely impermeable to exogenous and

endogenous substances that can potentially harm the brain[3]. Further, the BBB allows only approximately 5% of 7000 small-molecule drugs used for neurodegenerative disease treatment to cross the barrier[4]. Targeted temporary disruption of the BBB using FUS technology enhances drug delivery and accumulation, which could potentially improve survival outcomes for those suffering from difficult diagnoses such as GBM and other neurologic conditions. BBBO procedures can be used for several downstream applications, including targeted drug delivery to the nervous system, tumor ablation within brain tissue, and potential treatment for neurodegenerative diseases such as Parkinson's, Alzheimer's, Multiple Sclerosis (MS) and more.

During MR-guided FUS blood brain barrier procedures, it is vital that the patient's head be properly stabilized for safety and accurate targeting. Stereotactic fixation devices are common tools used to stabilize a patient's head in order to restrict extra movements during procedures. Unnecessary head movements can reduce the efficacy of the procedure at hand and, more dangerously, cause focused ultrasound beams to entirely miss the target tissue.

Currently, cranial fixation device designs are divided into two categories: stereotactic cranial frames and thermoplastic masks. Depending on the complexity and precision required of a procedure, a stereotactic frame or a thermoplastic mask may be utilized. This paper specifically seeks to explore the development of a novel stereotactic headframe for FUS applications. Head stabilization devices such as stereotactic frames that are currently being used for MRI-guided Focused Ultrasound (MRgFUS) applications are limited in that these frames were originally designed for general radiosurgery and stereotactic neurosurgery, making such frames suboptimal for FUS techniques. Additional limitations include the bulkiness associated with the frame design, which interferes with ultrasound beams and decreases the treatment envelope. Additionally, the stabilization method of current frames causes marked patient discomfort, as the placement of four pins into the cranium are necessary for keeping the head still.

Relevant Prior Art

The company Elekta has developed the Leksell Stereotactic System, which is intended for localization and diagnosis of intracranial disorders and surgical treatment in the context of radiosurgery and stereotactic radiation therapy. Within this system, the Leksell G-frame, as shown in Figure 1, is the existing model that is currently used primarily for Gamma Knife procedures. It is MRI compatible, and is typically composed of a titanium and aluminum alloy. The G-frame can be seen as a three-dimensional reference system based on the Leksell Coordinate frame, which has a semicircular arc and follows the center-of-arc principle. The concept behind the center-of-arc principle highlights that the target is always at the precise center of the stereotactic arc. As mentioned earlier, this frame is stabilized on a patient's head through the use of four fixation pins, which requires that the skin be pierced for access to a patient's skull. There are two pins located at the front of the patient's head, and two pins located at the back of a patient's head. MRI compatibility is also an important feature of this device, along with CT scanner compatibility. Another system, known as the Insightec system, is also used for BBBO and depends on a four-point fixation mechanism along with a rigid metal frame for cranial immobilization, similar to the Leksell G-frame.

In 2017, Elekta had also developed a new stereotactic frame design, called the Leksell Vantage Stereotactic System as shown in Figure 2. The newer design is manufactured in a glass fiber reinforced epoxy and uses FirmFix pins for head fixation on a patient's skull. These pins are made of polyether ketone plastic material, with a small aluminum tip that secures the head frame and Leksell Coordinate system to the patient. The composition of this frame is also MRI compatible and is less susceptible to image distortion than the Leksell G-frame. Like the Leksell G-frame, the new Leksell Vantage Frame is designed for head sizes that are 49 to 62 cm in circumference, in addition to accommodating for head widths ranging from 134-175 mm and skull front-to-back ranges from 167-215 mm. The Leksell Vantage frame has been shown to exhibit quicker assembly than the Leksell G-frame, along with

having easier to install pins that can stabilize the frame to the patient's head with better force distribution. Furthermore, the shape of the Leksell Vantage Frame allows for better torque distribution to ensure that the frame is less likely to be distorted under load. As seen in Figure 2, it is also evident that the design of the new frame is optimized for being more open-faced and lighter, with the goal of improving patient comfort during procedures. Although the new Leksell Vantage Frame presents a more streamlined design, there is still room for improvement especially in the area of patient comfort. This paper will outline the design process of a non-invasive, yet effective novel stereotactic headframe.

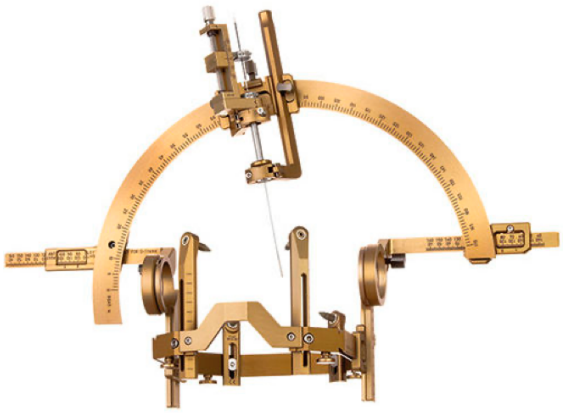

Fig. 1. The Original Leksell G-Frame. An existing frame used for Gamma Knife procedures. Note the semicircular coordinate system with precise markings on the arc.

Fig. 2. The Leksell Vantage Stereotactic System. A lighter, more streamlined design based on the Leksell G-Frame

Materials and Methods

Identification of Design Constraints and Specifications

All design iterations and considerations were made based upon certain structural and functional constraints that could limit certain aspects of the final design. The identification of these constraints was determined by conversing with several doctors and engineers working at the Focused Ultrasound Foundation, the UVA Focused Ultrasound Center, and the UVA Department of Neurosurgery. The first step in the design process involved visiting the Focused Ultrasound Foundation in Charlottesville, Virginia to examine the dimensions of the ExAblate Neuro Model 400 Type 2 ultrasound transducer with the help of Dr. John Snell. An image of the transducer is shown in Figure 3. It was crucial to measure the dimensions of the aforementioned transducer, as the procedure requires that stereotactic frames are able to fit within the transducer during a BBBO procedure.

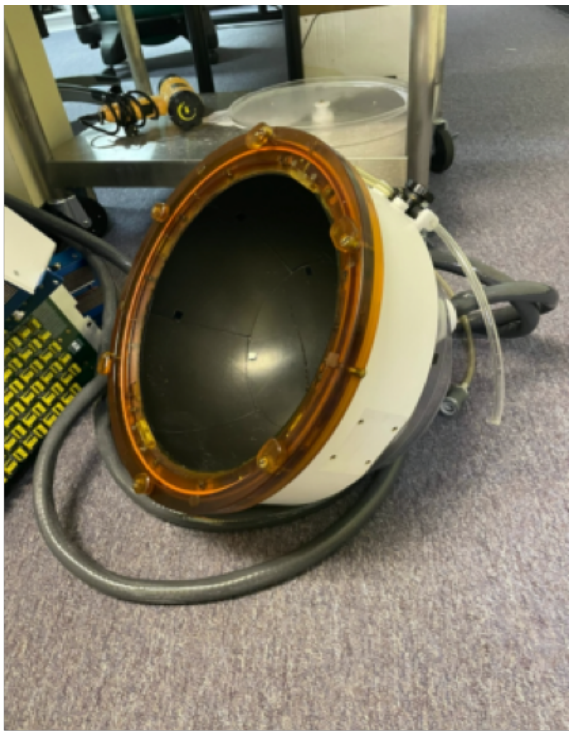

Fig. 3. The ExAblate Neuro Model 4000 Type 2 ultrasound transducer. This transducer has been developed by the medical device company known as Insightec, a company that sells MRgFUS equipment.

Within this apparatus, a patient's head is mounted and secured to the MRI bed in a fixed position in coordination with the stereotactic head frame to restrict movement during the procedure. A schematic showing the interplay between the Leksell G-frame, an ultrasound transducer, and patient positioning during the procedure is shown in Figure 4A. Additional design specifications are summarized in Table S1. Another important design constraint that needed to be accounted for prior to the design process was to ensure that the frame design is able to successfully interact with the patient bed, as shown in Figure 4B. Success of the design is heavily dependent on the ability of the frame to interact with the mount, as the mount is critical in keeping the frame intact and rigid during the stabilization process.

Creation of the Prototype Design and Physical Model

Design iterations of the novel stereotactic headframe were created using the computer-aided design software, Autodesk Fusion 360. A CAD representation of the base of the current frame was used as a reference template to commence the design process. The aforementioned representation was a good starting point for the new frame design, as this design had previously been the subject of simulations with the use of Kranion ®, an open-source and interactive transcranial visualization software designed for focused ultrasound. Kranion ® is an excellent software to obtain information related to geometric modeling, brain visualization, skull metrics, and an estimation of transducer efficiency. Based on the template, novel device modifications were made in fusion 360 in order to minimize image distortions, prioritize patient comfort, and streamline the design as a whole. The model of the base of the current frame and an image showing the interface of the Kranion ® simulation software can be seen in Figure 5A and 5B, respectively.

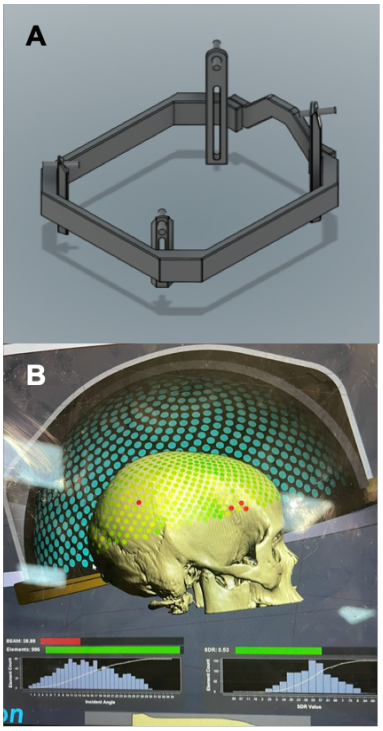

Fig. 5. Base Template and Software. (A) The base template for the design of a novel stereotactic headframe. (B) A visual of the Kranion ® transcranial visualization software.

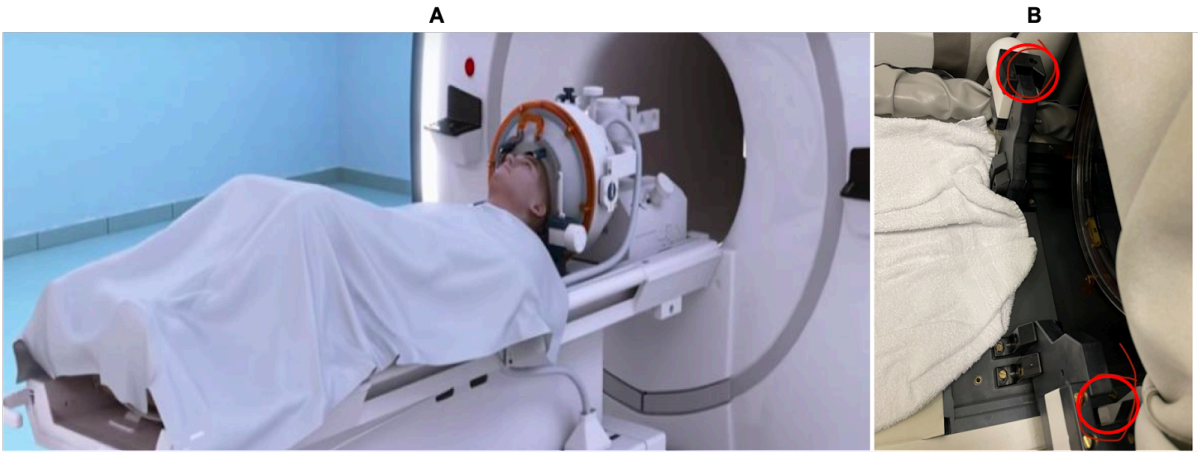

Fig. 4. Design Constraints. (A) A patient about to undergo a FUS procedure. The patient is fixed into position on the MRI bed with the headframe, which is interlocked into the FUS transducer. (B) The red circles highlight the mounting areas where the frame will have to attach prior to patient head fixation.

Design of a Tightening Mechanism

Assessment of the Initial Tightening Mechanism

Four pins are secured against a patient's head during the securing of the current headframe prior to procedure; the pins pierce the skin against four points of the skull, two in the front and two in the back, to prevent any possible movement of the head during treatment. This design concept was abandoned as the pins interfere with a membrane that is secured around the FUS machine against the patient's head during treatment. Additionally, the pins may increase patient discomfort during the attachment of the headframe due to the sharp points of the pins breaking skin at the points of fixation.

Exploration of an Alternative Tightening Mechanism

Many alternatives were considered as a potential replacement for the pins in the current headframe design. The current headframe utilizes pins to minimize movement to less than 1 mm during other radiosurgery procedures, as these procedures require extreme precision; the FUS procedure for which this novel device is being designed, the opening of the BBB, allows for a margin of movement of 2-3 mm. Due to this less restrictive margin, the pins were removed.

One alternative method explored for securing the novel device was a ratchet mechanism, similar to tightening mechanisms at the back of a bicycle helmet, devised with the help of Dr. William Guilford (Figure 6A)[5]. This mechanism would allow for ease of tightening, not penetrate the patient's head, and provide a secure, yet comfortable fixation. The ratchet mechanism was initially explored as part of a head-brace at the front of the headframe; this alternative, however, was not adequate for the purpose of this device due to its complexity and inability to glide smoothly with metal. The ratchet mechanism features numerous complex parts that would require testing prior to finalizing a prototype with the mechanism and requires a head-brace be placed around the top of the patient's head. This would cause more interference due to the placement of the tightening mechanism and the addition of a head-brace to the current model. Additionally, the ratchet mechanism glides easily with plastic, as designed in bicycle helmets, but would not glide with metal headframes; the wear and tear caused by consistent use of the headframe over time may also lead to poor performance of the mechanism.

The next alternative for a tightening mechanism was centered on the notion of simplicity. The head-brace from the previous ratchet mechanism was adapted as segmented bands in the front and back of the headframe; these bands would be smaller and thinner, to prevent any hindrance during procedures (Figure 6B). Using the concept of pins to secure the frame, four screws attached to the head-brace were devised as an alternative to apply pressure at the four corners of the skull to prevent movement of the head. The screws would be threaded through the front and back posts, along with nuts, and attached to the ends of the front and back head-brace. The head-brace would press against a patient's head as the screws are turned through the posts. The head-brace

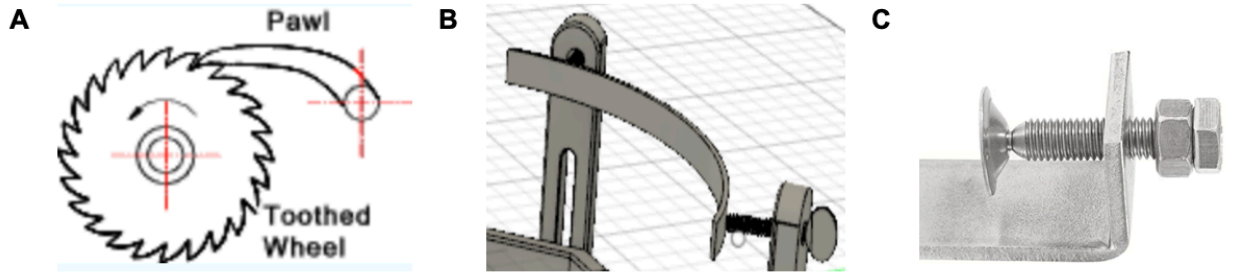

Fig 6. Alternative Tightening Mechanisms for Novel Headframe. (A) The ratchet mechanism, commonly found in bicycle helmets, is composed of two straps being pulled together by a toothed-wheel operated by a knob. (B) Front head-brace used to secure the head by holding the front and back in place securely. (C) Screw-and-nut tightening mechanism used in a C-clamp. The screw can be adjusted to go farther in or out, and the nut is tightened against the hole to secure the screw in place.

prevents movement, while preventing the screws from directly contacting the patient's head (Figure 6C); once the appropriate position is established, the screws will be secured tightly against the posts by tightening the nuts on the other side[6].

Alterations to the Current Model

The current headframe model used as a foundation for the novel device was thinned to reduce the bulkiness and weight of the headframe. The front nosepiece and back-piece were removed to further reduce the bulkiness and reduce the amount of material necessary for the frame. The novel device was constructed and simulated in CAD using a high-strength titanium alloy to compare against the current standard, however, other cost-effective and less bulky materials can be used for the proposed design.

3D-Printing the Final Prototype

The final design of the novel device was 3D printed using an Ultimaker 3 and an Ultimaker S3 printer with polylactide (PLA) material. The design was imported into the Ultimaker Cura program to adapt it for 3D printing and no significant changes were made to the design (Figure 7). The prototype was printed in 11 segments, which were attached together using hot glue (Figure 7). The screws were not 3D printed due to the minute details surrounding threading of the screw. Because compatible threading was not accounted for in the posts, the head-brace was attached to posts to mimic its initial position prior to adjustments from the swivel screw.

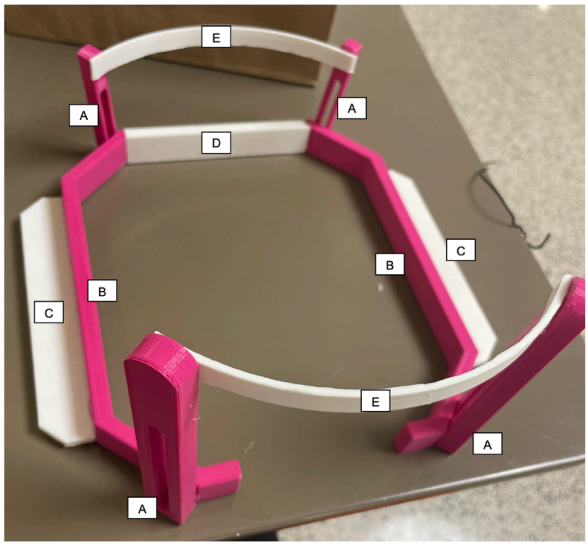

Fig 7. 3D-Printed Assembly of Prototype. The final novel device prototype was printed in 11 segments, the four posts (A), the two base pieces (B) and mounting wings (C), the back piece (D), and the two head-braces (E). The pieces were printed on an Ultimaker 3 and S3, using polylactide material in pink and white colors to visualize different parts clearly. The final assembly was joined together using hot glue.

Proposed Clinical Testing

Although the second phase of device testing was not able to be completed within the one-year project timeline, it is hoped that next steps can be accomplished to further progress this project. The first step involves purchasing the specific rotating swivel screws and incorporating it within the 3D-printed design to examine the adjustable component of the novel fixation device. The next step is to go through the IRB approval process for clinical testing; due to the amount of time needed for approval, it was not feasible to get the IRB approved within this project's timeline. After IRB approval, clinical testing is the most important step in the testing process. The goal of this project is to ensure that patients feel comfortable and at ease during a fitting procedure, and this metric is to be tested by bringing in patients with different head sizes and observing how the novel frame fits in accordance with each head size. Patient comfort is to be further analyzed through patient comfort surveys, where patients who have previously undergone a FUS procedure provide feedback on their comfort levels with the novel fixation device compared to old devices used for their respective FUS procedures.

Results

Final Prototype

The current device prototype features four main components: the base, the front and rear posts, the front and back head-brace, and four screws. The final prototype was assembled mimicking the assembly; however, the screws were omitted from the final structure due to limitations with the 3D printing (Figure 7).

Finite Element Analysis

Finite element analysis (FEA) was conducted in Fusion360 to validate the structural stability of the design under the forces applied on the fixation points when secured to a patient's head (Figure

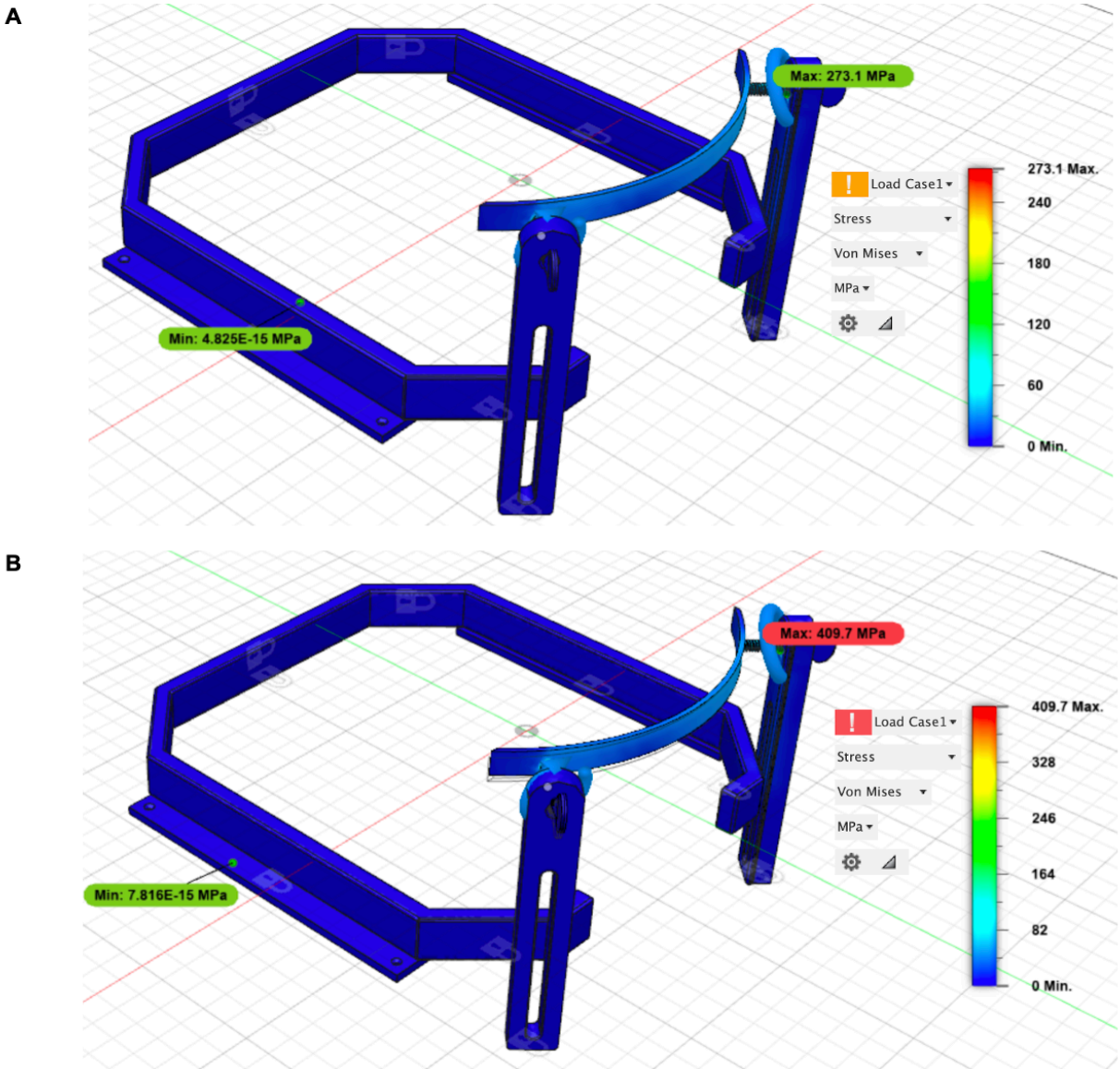

Fig 8. Static Stress Finite Element Analyses (FEA). (A) Static stress FEA conducted with an average torque value of 0.348 MPa applied to each of the two screws used for the fixation of the front head-brace. (B) Static stress FEA conducted with a maximum torque value of 0.522 MPa applied to each screw used for the fixation of the front head-brace.

8). The simulation was conducted on the design modeled with high-strength titanium alloy, similar to headframes that are currently in use. McMaster-Carr brand spade-head thumb-screw were selected for the four screws used for fixation due to their ease of use and cost[7]. Each screw is 1-inch long, with a diameter of 0.25-inch and ¼"-20 thread, to allow for a range of tightening lengths. The bottom, back, and both sides of the base of the model frame were constrained to simulate the securing of the headframe onto the focused ultrasound machine. Only the front head-brace was simulated to represent the forehead of the patient applying force against it; two pins were secured through holes in the front posts and attached to the head-brace. Structural loads were applied to both screws, an average torque of 0.348 Nm and a maximal torque of 0.522 Nm, representing the forces exerted against the head-brace during the fixation of the headframe (Figure 8A)[8]. Static stress analysis results showed that a maximum force of 273.1 MPa would be exerted on the fixation points modeled with the average torque value, with a safety factor of 1.01. A maximum force of 409.7 MPa would

be exerted on the fixation points modeled with the maximal torque value, with a safety factor of 0.67 (Figure 8B).

Discussion

Interpretation of Results

Focused ultrasound (FUS) is an early-stage, non-invasive surgical technology that affords the possibility of the treatment of various neurological disorders. Current head fixation devices, designed for use with general and stereotactic radiosurgery, utilized to secure a patient's head during FUS procedures are inadequate due to certain incompatibilities with the system[9]. The novel device described in this paper can effectively address some of the limitations of current head fixation devices in the context of FUS procedures. A streamlined headframe design that is thinner, without the nosepiece and back-piece, reduces the bulkiness and weight associated with current headframes. A sleeker design also reduces the hindrance caused by the use of a headframe during FUS procedures. The securing of the headframe using the head-brace attached to screws minimizes patient discomfort during the securing of the device as it does not penetrate the skin. Static stress FEA analysis of the final prototype of the novel headframe was tested using an average torque of fixation of 0.348 Nm and a maximum torque of fixation of 0.522 Nm[8]. This demonstrated a maximum force of 273.1 MPa exerted on the fixation points and safety factor of 1.01 given an average torque, and a maximum force of 409.7 MPa with a safety factor of 0.67 given a maximum torque. The prototype is capable of withstanding the force exerted on the fixation points given an average torque; given a maximum torque, the prototype will most likely deform, however, this is highly unlikely as the average patient will not exert the level of the simulated force. A safety factor of three or greater is optimal for the most structurally secure prototype, so further simulations are required to determine alterations to the design that would result in a higher safety factor. Additionally, the novel device has the potential of increasing the treatment envelope of the brain due to its streamlined design; simulations of the headframe conducted in Kranion® would be necessary to provide an estimate of the area of access for treatment. The cost of headframes provides a significant barrier to access; however, selection of low-cost, MRI-compatible material can address this limitation[10]. The long-term application of consistent pressure throughout various procedures is yet to be evaluated due to time and scale constraints. A prototype of the novel headframe composed of the aforementioned suitable material can be tested over a range of pressures and procedures with extended periods of wear to determine its longevity. The efficacy and compliance of the device can be determined through a clinical trial.

Impact

The development of a novel head fixation device that reduces ultrasound beam hindrance and increases treatment areas has many implications that can revolutionize cancer treatment. Opening the BBB with FUS provides an opportunity to get increased access to tumors within the brain, which increases the effectiveness of tumor ablation and chemotherapy drugs. With increased access to tumors, larger tumor volumes can be destroyed, which decreases the risk of cancer relapse and metastasis. Additionally, BBBO using FUS opens up the possibility for other neurological applications such as drug delivery to the nervous system for the treatment of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's, Alzheimer's, multiple sclerosis, etc[11].

Challenges and Limitations

Throughout device development, the team faced ongoing challenges in the context of ideation and design complexity. When considering the ratchet mechanism as a potential design solution, the team attempted to design all the particular parts of a ratchet mechanism similar to the mechanism used in bicycle helmets. The team used Google Patents to find engineering designs of bicycle helmet ratchet mechanisms, and after a month of attempting to design a simplified ratchet mechanism based on the aforementioned patent, the team decided to forgo such a complex design plan and focus on a much more simplified design given the time constraints. Unfortunately, the time spent in the ideation phase was prolonged

more than expected which delayed the project timeline.

Lack of timely awareness and familiarity with IRB approval procedures also impacted the clinical testing phase. Since the team was focused on the ideation and design phase for a considerable amount of the timeline, attempting to get IRB approval would not have been feasible within the capstone deadline. The next steps of this project, thus, involve getting IRB approved before moving on to clinical testing, since clinical testing is a crucial component to test fitting of the stereotactic head frame, and in turn, patient comfort.

Opportunities for Future Development

A current problem related to head fixation devices is the issue of cost and accessibility. Current headframes such as the Leksell G-frame cost anywhere from $10,000 - $30,000, which is a hefty price tag for many hospitals. In order to allow patients of various income backgrounds to be able to undergo FUS treatment, it is important for lower-end hospitals to be able to afford stereotactic frames. By pinpointing a material that is not only MRI compatible but cheaper than the rather expensive materials used for current frames, stereotactic frames can be distributed to a far broader audience. Increased distribution has the potential to save far more lives that suffer from conditions such as GBM and other deadly conditions.

Another area where future development lies is in further ideations of the stereotactic frame for applications that require far better stabilization prior to a procedure. BBBO is a treatment that can tolerate up to 2-3mm of head movement. However, procedures that require precise tumor-ablation techniques tolerate far less head movement during the procedure. Thus, the novel stereotactic frame could be further iterated upon to ensure very minimal head movement. Furthermore, these experiments could extend to thermoplastic mask design as well, as masks are also used as common fixation devices[12].

End Matter

Author Contributions and Notes

Bhatia, I. and Kormath Anand, R. conducted extensive research prior to ideation, created CAD designs, constructed the prototype after 3D printing and conducted finite element analysis on the design assembly. The authors declare no conflict of interest.

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Supplementary Information

Design Constraint/Metric	Unit of Measure	Marginal (Acceptable)	Ideal Value
Diameter of the transducer system	Millimeters	300	300
Outer ring of the outside of the transducer	Millimeters	15-16	15.45
Middle ring of the inner of the transducer	Millimeters	13-14	13.19
Inner ring of the transducer	Millimeters	10-11	10.38
Fixation device mounted to bed	Millimeters (Range of motion)	0	0
MRI compatibility	Material	MRI Safe/Compatible	MRI Safe + Does not appear in image scan.
Average available range of treatment envelope. (Reduced width and lowered position of rungs on fixation device)	Percentage	75-100	100
Frame thickness	Centimeters	0.5-1.5	0.5
Head sizes (head frame that accommodates different head sizes)	Centimeters	49-62	49-62
Range of head movement allowed	Millimeters	2-3	2
Load supported by frame	Pounds	15-25	25

Table S1. Design Specifications. The design specifications and constraints listed above were considered prior to the ideation and design phase