Systematic Procedure for Transitioning Intracranial Hemorrhage Treatment from CT to MRI Guidance

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Purpose: To fabricate and validate an intracranial hemorrhage (ICH) model which behaves dynamically, appears similar to clinical ICH under MRI scanning and does not use metal materials. This model will be used to prove the advantages of ICH treatment in Magnetic Resonance Imaging (MRI) over the currently used Computed Tomography (CT).
Materials and Methods: An agarose gel (Sigma Aldrich), sodium polyacrylate hydrogel (Super-Sorber, Newstone), LDPE membrane (Ziplock), and veal blood was used to create the ICH model. The veal blood clot was aspirated under MRI in order to validate model behavior.
Results: The model was successful in reducing clot volume through the removal of plasma. The components of the clot were reduced from 77% plasma to 8% plasma, leaving 92% of the clot to interact maximally with administered rtPA. .
Conclusion: The created ICH model behaved appropriately when aspirated under MRI conditions. With further testing the model could open the door to animal testing and eventually clinical trials.

Graphical Abstract

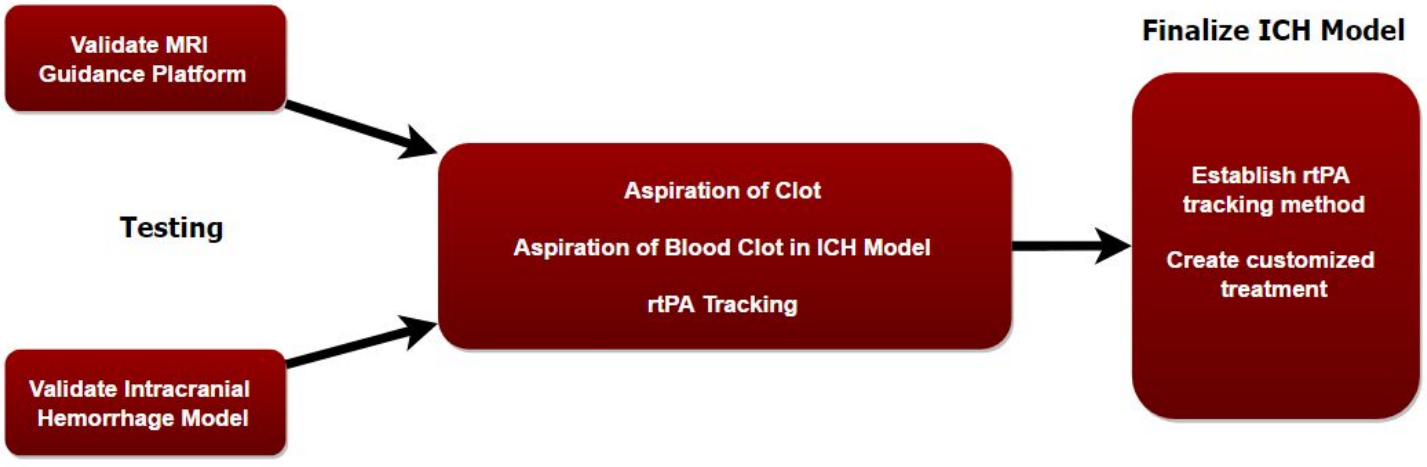

Figure 1: It is the hope of the group that this model will aid future improvements in ICH treatment and perhaps facilitate the development of an rtPA tracking method within the clot itself.

Highlights

1. The aim of this project is to develop a model which successfully mimics ICH clot reduction.
2. The model should also have similar imaging properties to that of ICH clot under MRI.
3. This model can be used to better predict clot characteristics and improve patient care.

Introduction

There are two types of strokes, ischemic and intracranial hemorrhage (ICH). These devastating medical events affect hundreds of thousands of people unexpectedly each year, 10,000 people in the United States alone. The more common ischemic strokes occurs due to an occlusion within the brain's vasculature, resulting in a loss of neurological functions dependent on the region of the brain affected. While ICH only accounts for 10-15% of strokes, it is more devastating than ischemic stroke. ICH occurs due to a failure of the vascular wall and an expulsion of blood into the parenchymal space. As much as 60 mL of blood can gather in the brain, which greatly increases intracranial pressure [1,2]. The shear volume of blood and increased pressure causes immediate neurological deficits, coupled with secondary chemicals released due to the breakdown in the blood-brain barrier. The released blood forms a two part clot, a fibrous (solid) part which covers the hemorrhage site to stem bleeding. The second part is a pool of liquid plasma left behind as the blood clots, surrounding the fibrous portion. As mentioned, ICH occurs less frequently than ischemic stroke but has a significantly higher rate of mortality. Patients who are survive the stroke have little prospects for rehabilitation, and typically require assisted living for the rest of their lives [3].

Currently, there is little that can be done for victims of ICH. To date, one of the largest and most successful studies to treat ICH was the "Minimally Invasive Surgery plus rtPA for Intracranial Hemorrhage Evacuation", better known as the MISTIE trials. This research study used computed tomography (CT) to image the clot and estimate size and location. Ultrasound was then used to guide a catheter into the clot administer a recombinant tissue plasminogen activator, or rtPA, to break down the fibrous the clot. rtPA activates the fibrinolysis pathway which lyses the fibrous portion of the clot so that it can be removed. The aim of the study was to provide a better understanding as to how the clot reacted with rtPA, as well as insight into how a physician's approach affected the outcome. The MISTIE trials were able to reduce clot volume by one half on average, although the results were incredibly variable as shown in Figure 2a. The variability of results can be attributed to the fact that each patient was treated with identical protocols despite a variety of clot characterizations. Every patient suffers from a clot of different size, shape, location, and mechanical qualities. Clot properties of each individual patient must be understood in order for personalized and accelerated treatment [4]. The success of the MISTIE trials has demonstrated that administration of rtPA into a clot volume can reduce clot volume and therefore reduce neurological deficits. The study did leave a large window for improvement, and reduction in variability. The team has a vision for treating ICH with an improved imaging modality, namely MRI.

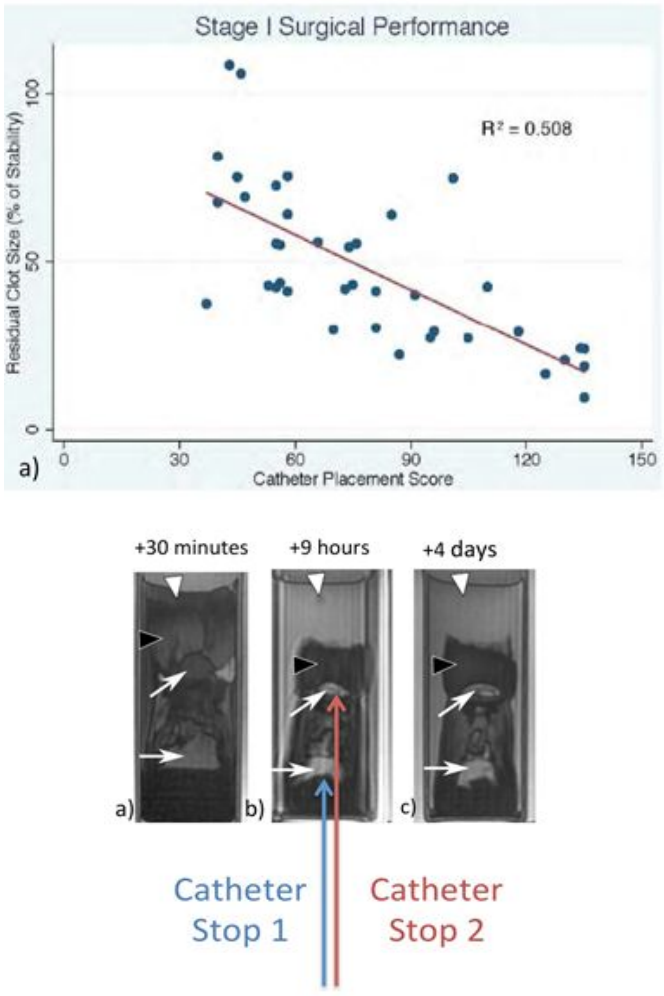

Figure 2: (a-Top) Surgical Performance of MISTIE Trials. (b-Bottom) Vial of clotted blood imaged in MRI.

If the imaging modality of ICH treatment can be transferred from CT to MRI, the MISTIE trials can be greatly improved. MRI can image soft tissue such as a blood clot in the brain with higher resolution than X-ray based CT. Figure 2-b shows vials of clotted blood imaged with MRI. The lighter grey portions of the clot are pockets of plasma. Under MRI guidance the surgeon can drain the plasma regions first and then administer rtPA. This allows the rtPA to have maximal direct interaction with the fibrous clot. The rtPA will not be diluted by the surrounding plasma as it is with the current MISTIE trials.

In order to move ICH treatment into MRI, a standard model must be developed and used to quantitatively show the benefits of ICH treatment under MRI. Trials could then move on to animal and finally clinical trials. The criteria for designing the model are that the model must behave dynamically, replicating change over time as would the brain during actual treatment. It was also essential that the administered rtPA not leak out of the clot region and into the model. rtPA is incredibly expensive and leaking would be wasteful. Additionally, the model could not use metallic components due to the magnetic field generated by MRI.

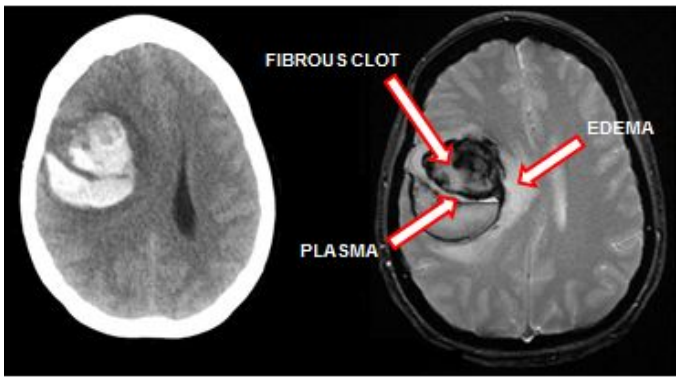

Figure 3: CT (left) and MRI (right) images of a brain clot [1].

The design team initially decided maintaining the model in a body temperature environment was essential to the functionality of rtPA. However, additional research showed that using rtPA at room temperature only results in a 20% decrease in functionality [5]. The client deemed this to be an acceptable decrease in functionality, especially since the focus of the project was to create a model, not evaluate effectiveness of rtPA. Another important physiological element that this model must replicate is pressure. While the standard pressure of a human brain is anywhere from 5-15mm, the pressure reached in the model is not important, per our client, as long as the mechanical characteristics of the model are retained [4]. The dynamic movement of the material is the primary mechanical characteristic of interest; the model must be able to successfully collapse upon the clot as it is drained. The collapse could be created by an external force or by the weight of the model itself.

Materials and Methods

Before testing a model with animal blood it was important to test the prototype with a different substance, in order to avoid sacrificing animals before the model was fully functional. Secondly, testing with a different substance first allows the team to become familiarized with the testing protocol and familiarize and procedure. The team decided that oil and water would distinctly separate in the model, much like the fibrous and plasma portions of clotted blood. This minimized the chance of making mistakes when using animal blood that would have the potential to corrupt data and waste valuable blood material.

The final procedure was written for testing with animal blood, and for the first trial, a LDPE bag filled with oil and water substituted a real animal blood clot. In the procedure, an agarose gel is formed around the LDPE bag to hold it in place during aspiration. A layer of hydrogel is added on top of the agarose to displace any volume in the model that is extracted during the aspiration. This material is important. If it is not incorporated into the model, air instead of hydrogel would accumulate around the LDPE bag during aspiration which would distort the MR-image and render the images useless for quantitative analysis. The procedure for creating the ICH model can be found in Appendix A.

Validation of the model using an oil and water clot allowed the team to move ahead to testing with animal blood. A detailed protocol for model construction is included in Appendix A. Fabrication of the clot itself was the first step, utilizing LDPE (Ziplock) to surround and contain the animal blood. LDPE is able to adhere to the surface of the catheter or syringe when punctured, preventing clot material and any administered rtPA from

leaking into the surrounding model. Additionally LDPE is pliable enough to allow easy entry of the catheter or syringe into the clot. Veal blood obtained from a local animal sacrifice facility was placed into an LDPE bag and sealed. The clot was then suspended in an agarose gel (Sigma Aldrich) solution prior to allowing the agarose to solidify. Suspension of the clot in agarose is essential; prior testing revealed that embedding the clot within a mechanically stable layer was necessary. Without this support the clot would simply move around within the model, and the surgeon would be unable to puncture the LDPE bag to aspirate the clot. Agarose was selected since it has similar mechanical properties to that of the brain [6]. Once the agarose hardened, the clot supports could be removed, leaving the clot suspended in agarose. Finally, a hydrogel layer consisting of water and sodium polyacrylate (Super-Sorber, Newstone), a common hydrogel, is placed over the top to act as the dynamic layer. The hydrogel can behave dynamically because the structure is not crystalline, allowing the material to easily collapse into the void generated during clot aspiration.

Dr. Block's affiliation with the Wisconsin Institute for Medical Research (WIMR) allowed the team access to a 3T research MR Scanner. An imaging protocol (Sag_CUBE_T2_maxTE) was run and MR images gathered for the model both before and after clot aspiration. Figure 4 (top) displays the model before clot aspiration. MR imaging distinctly reveals differences between the fibrous (5) and plasma (4) regions of the clot. A total of 44 mL of plasma was aspirated from the model. A imaging sequence run after aspiration, Figure 4 (bottom), displays the success of the model. The hydrogel (1) has filled the void created by the aspiration and surrounds the LDPE membrane (3) as well as the remaining fibrous clot.

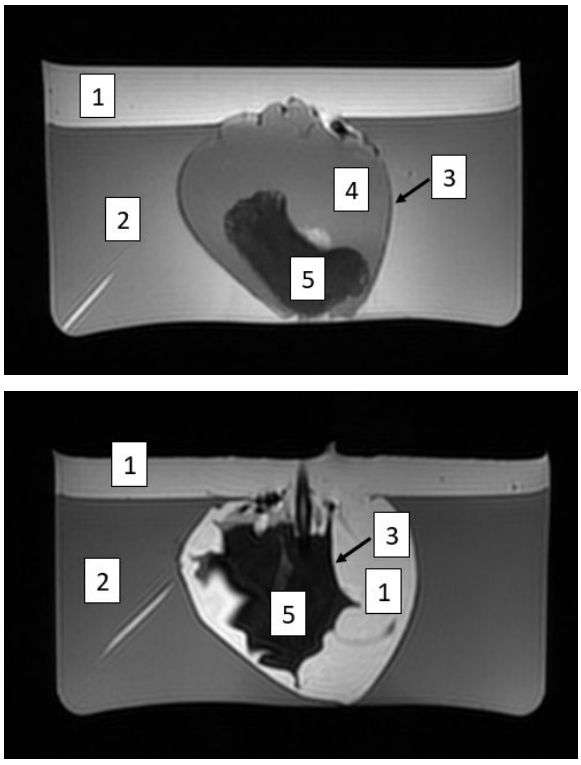

Figure 4: *MR image of prototype before clot aspiration (top) and after aspiration (bottom). Hydrogel(1) filling in the void as plasma aspiration is visible. Materials of the images are as following : 1) Hydrogel 2) Agarose gel 3) LDPE membrane 4) Plasma 5) Fibrous clot*

Figure 5: *Image of the ICH model post-aspiration as it was placed inside a coil meant for MRI head scans.*

Results:

After completing the clot aspiration under MRI, the team was able to conduct a volumetric analysis of the clot using a program called ITK snap. Figure 6 contains a 3D rendering of the clot before aspiration (top) and after aspiration (bottom). The blue region represents the plasma region surrounding the red fibrous clot. Prior to aspiration it is clear that the majority of the clot consists of plasma. After aspiration only a small portion of plasma remains, leaving the fibrous clot exposed for rtPA interaction. ITK Snap also allowed the team to calculate the volume of both the plasma and fibrous regions by thresholding the distinct line between the fibrous clot and plasma, as well as between the clot and the hydrogel region as shown in Figure 4. Table 1 contains the results of this volumetric analysis, which is graphically represented in Figure 7. Prior to aspiration the clot was composed of 77% plasma, while post aspiration only 8% of the total clot was plasma. A clot consisting of 92% fibrous regions exposes the fibrous region to the maximum amount of rtPA exposure.

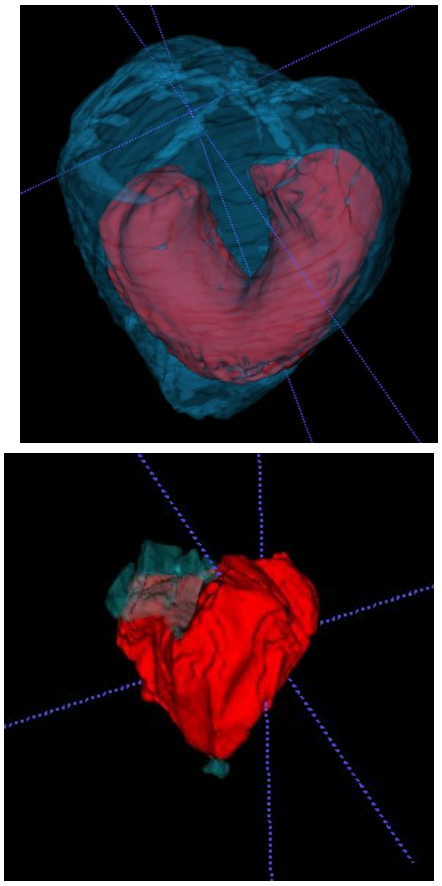

Figure 6: *Visualization of before (top) and after (bottom) the clot aspiration using ITK snap. The red portion illustrates the fibrous clot while transparent blue represents the plasma. Clot shrinkage is apparent with reduced plasma after the aspiration*

Procedures	Total	Plasma	Fibrous
Before Plasma Aspiration (mL)	58.89	45.16	13.73
After Plasma Aspiration (mL)	13.251	1.081	12.17
Decrease in Volume (%)	77.5	97.6	11.4

Table 1: *Volumes calculated from volumetric analysis of MR*

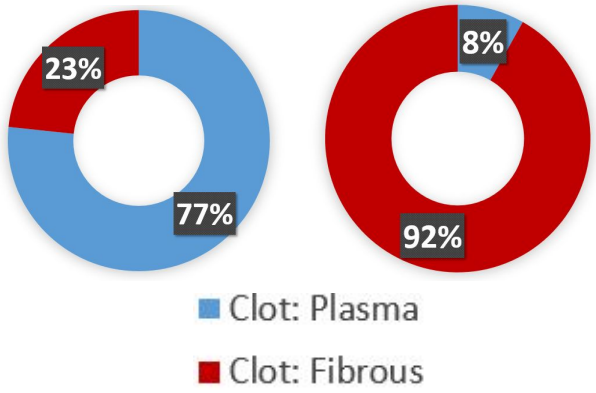

Figure 7: *Only one trial was performed using the prototyped model. The circle graphs show that aspiration was effective at removing excess plasma, leaving behind only 8% of removable plasma.*

Discussion

The most important design criteria for the ICH model was its ability to collapse when a void is created. Other design criteria including pH, temperature, and mechanical properties were deemed unimportant due to its negligible variation throughout the procedure. For example, decreasing the temperature from body temperature to room temperature, a difference of 14 °C, causes rtPA to lose 20% functionality [5]. It was not necessary that the model mimic mechanical properties of the brain, however the agarose material used exhibits similar properties to that of brain tissue. The team conducted an aspiration sequence to validate the model. During testing, plasma was removed, causing an area of negative pressure to form. The material properties of hydrogel allowed it to easily flow into the void as seen in Figure 4.

From a qualitative, visual standpoint, this behavior validates the desired collapsibility characteristic and mimics images during an actual ICH event. In terms of quantitative data, the amount of plasma removed from the total blood clot was significant. Total clot composition before aspiration consisted of 77% plasma and 23% fibrous clot. After aspiration the total clot volume consisted of 8% plasma and 92% fibrous clot. The 45.639 mL decrease in total clot volume extremely important; not only does the decrease in plasma volume immediately decrease pressure for the patient but it could also decreases treatment time. This possible decrease in treatment time stems from the ability of rtPA to act on the maximum surface area of the fibrous clot portions. Clot aspiration and rtPA administration under MRI does not allow the rtPA interaction to be wasted on reactions with plasma portions of the blood. Overall the model behaves like a true ICH event. With the model validated for desired characteristics, next steps will consist of using it as a gateway to transition to MRI treatment of ICH. Validation through animal trials will eventually lead to clinical trials and finally patient ICH treatment.

Limitations

The team had access to many resources and experts throughout the development of an ICH model. However, there were several significant limitations, mainly time, cost and accessibility of materials. Firstly, due to the time scale of the project the team is limited to few months to complete testing and analyze the results. Given more time the team would have conducted more trials to increase statistical reliability and conduct an in-depth analysis of the results. The project was reliant on availability MRI scanners to collect data. Collaboration with our client and the Wisconsin Institute for Medical Research was key for obtaining access to scanner time. Through a grant given to Dr. Block, the time spent on MR scanners required no out of pocket expenses for the design team. However, reserving the scanner often required research to be delayed up to two weeks due to unavailability. Research scanners at the WIMR are in high demand for use by other researchers. Access to rtPA was a significant limitation to the success of this project. rtPA is very expensive and can cost upwards of $330 per trial. Ultimately, the team did not have the opportunity to conduct testing of regarding clot lysis within the model due to this cost. The final hurdle was obtaining blood for testing, which comes from a sacrificial animal testing laboratory on campus. It is difficult to reserve quantities of blood since the lab has a schedule that they follow. This schedule was often not conducive with the team's desire to test, and delayed testing by over a week. Of course obtaining blood alone is not the only consideration, but also handling and disposal of the material as well. Proper regulations must be adhered to as well as general safety guidelines. Because many of our experiments are not dependent on the properties of blood to show the viability of our design, blood was often replaced by a surrogate material.

Future Work

While our team successfully demonstrated the promise that MRI has in the ICH treatment realm, there is more to be done. Our model, while effective, was very simple and lacked the complexity found in the real life scenario. Ideally we will move forward by creating a more replicable clot holder. A preliminary SolidWorks design, Figure 8, was created so that the model could be 3D printed. This model establishes a standard that can be 3D printed by any research lab. The design consists of four stabilization screws, two access screws, and one filling screw. The four screws around the perimeter allows for stabilization of the two halves, sealing both together. The larger center hole in the top view allows for an access point for insertion of the catheter. The bottom view also has a larger second opening, creating another access point. The smaller center screw allows for filling of the model with hydrogel. The final model would be fabricated of a dense plastic material that will not negatively affect the MRI image

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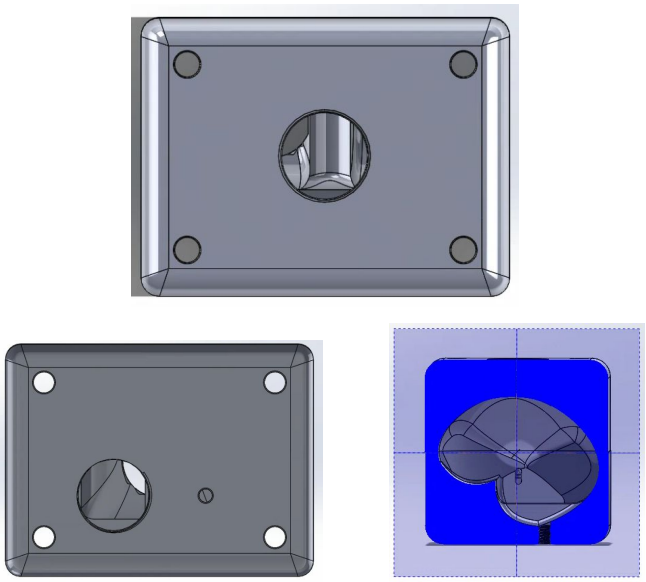

Figure 8: Top (top view), Bottom Left (bottom view), Bottom Right (cross section).

In addition to creating a new clot holder, the team would like to expand on our testing protocol to include not only analysis of plasma aspiration, but also continue on to study how our model handles rtPA administration over time. This would provide a better picture as to how our model behaves in a scenario similar to the real procedure, giving our research more reliability. From this the team will be able to draw stronger conclusions as to the success ICH treatment would have in the MR imaging modality.

Conclusion

Intracranial Hemorrhage treatment in CT is outdated and inept at treating patients when compared to the potential of the possible MR treatment. The basis of this claim can be found not only in theoretical practice, but also in preliminary research in the results of the MISTIE trials. These trials successfully showed that the surgery is quite dependent on the individual skill of surgeon. Whether it be the placement of the catheter, or the interpretation of the CT scan, the amount of variance found in current ICH treatment is excessive and unnecessary. The precision with which the Physician is able to place the catheter into the intracranial clot is dependent on the imaging modality provided by which is used. In CT, clot imaging is non-distinctive and appears homogenous despite highly distinctive regions within. In CT, it is difficult to distinguish different states of the blood, and therefore information provided to the physician is not adequate enough to optimize catheter placement. Unlike CT, MR is quite capable of displaying highly descriptive images of the clot. As can be seen in Figure 3, difference between imaging modalities is quite significant. By using MR imaging instead of the images provided by CT, the physician can make educated decisions regarding catheter placement and rtPA administration. This will directly lead to more clot being drained in a shorter amount of time. Ultimately, this transition would create a more customized and safe procedure for the ICH patient. Our model proves that immediate patient relief can be provided by the removal of the surrounding plasma before rtPA is even administered at a faster rate in MRI than CT. Also, physicians currently treating ICH in CT can use our model to practice and perfect the treatment techniques required in the MR environment. No current models exist which replicate the collapse of brain tissue onto a draining clot, so our model can create a basis by which the medical field can begin to evolve towards MR treatment plans. It is clear after observing the clear benefits of MRI and the success of this model that ultimately the patient's outlook will be improved, and more people will walk away from this possibly life ending occurrence. MRI allows for better visualization of clot components which allows for a more aggressive clot reduction approach and a greater ability to monitor rtPA administration.

References

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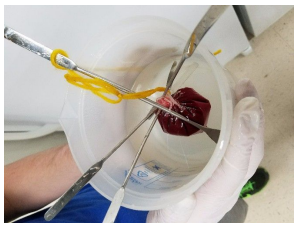
Appendix A : ICH Model Creation and Clot Aspiration Procedure

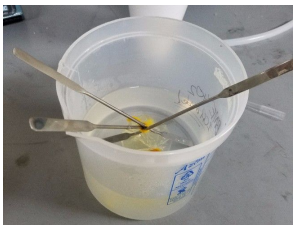
1. *Obtain the following materials:*
    a. 2 Low-density polyethylene(LDPE) bags (Clot Holder Material)
    b. 0.80 g of sodium polyacrylate hydrogel
    c. 1 empty syringe (syringe 1)
    d. 5 inches of string
    e. 50 mL graduated cylinder
    f. 2 g agarose
    g. 250mL Erlenmeyer Flask
    h. Microwave
    i. Weigh boat
    j. Hot rubber hand protection (for handling hot flask)
    k. 1 Scoopula
    l. 1 Plastic bag
    m. 1 Plastic beaker (1L)
2. *Prepare agarose gel*
    a. Add 0.2g agarose to erlenmeyer flask
    b. Add 200mL deionized water to erlenmeyer flask
    c. Swirl solution for 30 seconds
    d. Place in microwave on high for 1 minute
    e. Once solution begins to boil, stop heating, remove from microwave, and swirl for 30 seconds
    f. Place back in microwave and repeat step (e) until agarose powder is completely dissolved.
    g. Add agarose gel into a 1L plastic beaker:

3. Pour agarose gel into plastic beaker.
    a. For oil/water test (trial 1)
        i. Pour 30 mL of water and 30mL of vegetable oil into LDPE bag
        ii. Squeeze out any remaining air in bag and then seal completely.
        iii. Twist bag 6 times and secure with slip knot - ensure all of the liquid is captured.
        iv. Cut off bag remaining bag above the knot. The result should look like this:

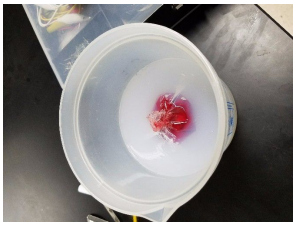
    b. For final testing (Blood Clot)
        i. Obtain animal blood clot (~60 mL) and add to the corner of a plastic ldpe bag.
        ii. Squeeze out any remaining air in bag and then seal completely.
        iii. Twist bag 6 times and secure with slip knot - ensure all of the liquid is captured.
        iv. Cut off bag remaining bag above the knot. The result should look like this:

4. Place LDPE bag into agarose liquid and secure each 3in length of string to the sides of the plastic beaker for support. Use scoopula utensils to hold bag in center of gel if necessary (recommended).



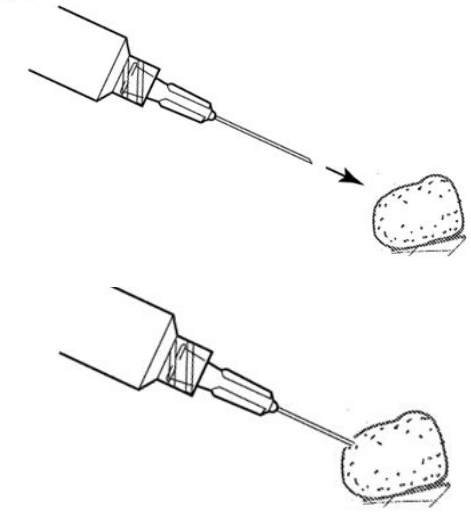


5. Allow agarose to cool for 1 day or until gel becomes hard
6. Remove scoopula utensils if used to secure LDPE bag in place.



7. Pour 0.40 g of sodium polyacrylate into plastic beaker container.
    a. Add 50 mL of water at a time - stirring each time to mix the hydrogel - until 100 mL is added to the model.
8. Ensure no air bubbles appear in the gel and move model into the MRI bore.
9. Begin acquiring MR images to identify areas of clot that plasma occupy
10. Acquire an empty syringe and insert its needle tip into the blood clot plasma pockets (pictures below shows the LDPE bag and syringe. It is assumed that the LDPE bag is surrounded by agarose and hydrogel).

(1)



11. Drain plasma pocket using the syringe.
    a. Slowly pull the plunger of the syringe outward.

    b. If plunger becomes hard to pull, stop immediately, reposition syringe tip, and pull gently again to extract more plasma.
    c. Once there plunger consistently becomes hard to pull after repositioning tip multiple times (5 or more), most of the plasma will have been extracted.
12. Confirm that plasma has been drained with MR images.