

A Mathematical Modification to Cryosurgery

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Abstract

Cryosurgery has many negative aspects, but the one thing that turns people away from the treatment is the risk of potential harm to healthy tissue. This risk has caused cryosurgery to be considered extremely risky in areas close to sensitive nerves, which are usually the areas that could use the treatment the most. In order to fix the problem and lessen the risk of damage to healthy tissue, one would need to discover a way to find the specific amount of liquid nitrogen that should be used for every size tumor. One can discover such a way by modifying the dilution equation by adding in variables that can be found more easily and creating a new equation that can easily be used to solve for the specific amount of liquid nitrogen that should be used for a specific sized tumor. With the new equation figured out, one can move onto testing different bacterial cultures by solving for the specific amounts of liquid nitrogen that should be used and recording the amount of leakage for each cell culture. After conducting this experiment one will discover that the risk of harm to healthy tissue is decreased to 7.5 % of the entire area (including the area of the frozen culture and the area of the leakage). In other words the leakage is only able to spread less than .1 centimeters away from the frozen area.

Background

John Bryce, a medical doctor, once said “Medicine is the only profession which works continually to eliminate its existence” (The Doctor’s Page, 2005). For years, medical professionals have been on a never ending search for cures to the world’s deadliest and most incurable diseases. Although nearly all of their experiments and research studies have failed to produce a favorable outcome, the information gained along the way has built a platform for others to continue to search for cures in the future. Still, more often than not, the outcomes branching from these clinical trials and research papers can be combined to help create a treatment for a common cause. By combining cryosurgical analysis, cryo probe design, and dilution techniques a new form of treatment can be created in order to help lessen the risk of harm to surrounding healthy tissue during a cryosurgery procedure.

In 1851, Doctor James Arnott of the Middlesex Hospital began to treat enlarged tumors with a mixture of salt and ice, hoping to find a new cure by observing the reduction of hemorrhage, pain, odor, discharge, and tumor size (Braithwaite, 1861). Although his intentions were only meant toward curing enlarged tumors, his work lead to the discovery of cryosurgery in later centuries. Throughout the decades after Doctor James Arnott’s death, thousands of doctors have modified his study hundreds of times until they discovered the form treatment used today. In modern medicine, cryosurgery is a procedure which uses liquid nitrogen, argon gas, carbon dioxide, or nitrous oxide to freeze and kill diseased tissue (Pfenninger and Fowler, 2003). Today Doctor James Arnott’s procedure has become a form of treatment for diseases such as kidney tumors, cervical cancer, prostate cancer, and skin lesions. Even though Doctor Arnott’s procedure has disappeared and been replaced over the years, his work has allowed millions of

lives to be saved as new treatment options, branching from his ideas, become available to those in need.

Cryosurgery is used to treat an assortment of diseases worldwide through a single procedure that modified easily as changes become necessary to make. Unlike many other surgical procedures, cryosurgery requires little to none pre-procedure patient preparation, making the task easier on both the patient and the surgical team. Although the patient requires little preparation, the surgeon must consult with the patient's physician and decide on a few important aspects involved with the procedure, depending on the location and size of the affected area. For starters, the surgeon must decide which freezing agent is suitable for freezing the tumor or lesion while still keeping the patient safe enough to make it through surgery. Albeit liquid nitrogen and nitrous oxide are the two most common freezing agents used during cryosurgery, a surgeon will likely choose liquid nitrogen over the other because liquid nitrogen is able to achieve the desired freezing levels eight to ten times faster than nitrous oxide. Once the appropriate freezing agent is selected the surgeon must move onto choosing which method is both safest and most likely to produce the best outcome, on which to deliver the liquid nitrogen to the diseased tissue. There are two ways in which the liquid nitrogen can be delivered: either through a cryogun spray technique or through contact probe technique. These two methods follow nearly the same procedure; however, the cryogun is used on larger tumors where as the contact probe is used in highly sensitive areas where excess spray must be avoided. If the surgeon were to choose the cryogun method he would then have to choose the appropriate nozzle size, depending on the size and location of the tumor. Usually a surgical team will start out using the pointed tip nozzle as it acts as a starting point when measuring the size of the infected area. If the nozzle appears too small to cover the top of the tumor then the nozzle may be replaced with a slanted flat tip nozzle

which has a larger orifice size and can treat larger lesions faster. However, if the slanted tip nozzle is unable to cover the top of the tumor then the next size nozzle, a hemorrhoid tip, can be used. Once the correct nozzle is selected the surgeon can proceed by making a small incision, large enough to expose the lesion, and begin the spray of liquid nitrogen (applied at -196 degrees Celsius or -320.8 degrees Fahrenheit), which covers an area of about 3 to 4 centimeters. Once an ice ball begins to form the surgeon can remove the spray and close the surgical field. On the hand if the surgeon were to have chosen the contact probe as the more appropriate method of treating the tumor, he would have followed the same method as the cryogun, yet everything would have been down scaled to about 2 to 4 millimeters. Although the two methods of delivering the liquid nitrogen are used to treat different sizes of tumors and lesions, their impact on the infected areas begin the same process of forcing the diseased cells in to cell suicide (Sutton, 2008).

When it comes to cryosurgery, the instrumentation used and procedure followed are only half of the process of destroying the diseased tissue. After the instrumentation delivers the liquid nitrogen to the surgical field the biological chemistry of the body begins to take effect. Once the cells reach a temperature of -2.2 degrees Celsius they begin to freeze, becoming super cool around a temperature of -5 degrees Celsius. Although the cells are beginning to freeze their nucleus allows them to recover even at these cold temperatures, therefore, the tissue must reach a temperature between -10 degree Celsius and -20 degrees Celsius in order for the liquid nitrogen to begin tissue destruction. When working with malignant tumors a deeper freeze, usually between the range of -40 degrees Celsius and -50 degrees Celsius, is used to insure that the cells are completely destroyed. As the cells are frozen at these specific temperatures they begin to be forced into cell suicide for reasons unknown to scientists and doctors alike. One theory suggests

that the concentrated solutes in the extracellular freezing area cause dehydration, damage to the enzymatic system, and destabilization of the cell membrane making it impossible for cells to regenerate themselves. However, it is a known fact that intracellular ice becomes water trapped inside the cell when thawing occurs rapidly resulting in osmotic disequilibrium and causing injury to both the intracellular structure and membrane of the cell. Also the freezing alone induces vessel wall injury either to the cell directly or to its structure causing no blood to be able to flow freely and easily throughout the cell thus leading to a lack of nutrient causing necrosis, which is the premature death of cells and living tissue, in the frozen area. As the cells are forced into cell suicide the size of the ice ball forming around the infected lesion must be watched carefully as the size of the ice ball is the most important criterion in determining how long to freeze the cells. If the cells are frozen too long, the liquid nitrogen can spread to healthy tissue and cause permanent damage to the body. Cryosurgery is a procedure which combines the use of the human mind through instrumentation and the body's natural reaction to its environment (Pfenninger and Fowler, 2003).

The process involved in cryosurgery, even though very risky as many factors must be watched with accurate precision, has some advantages which make it a great alternative for those whose tumors or cancers are unable to be treated with regular chemotherapy or radiation treatment. For instance, one of the most beneficial aspects of cryosurgery is that it is a minimally invasive procedure which has minimal blood loss and can be done as an outpatient procedure. Since the surgery has a shorter recovery time and can be performed as an outpatient procedure, the surgery as a whole usually costs less than the traditional treatment that would have been prescribed. However, another advantage of the procedure is that if the surgery were to fail then it can easily be performed again and if necessary radiation therapy and radical surgery is still an

option. Recent studies have shown that outcome of primary cryosurgery for prostate cancer was around 80 percent and the outcome for renal tumors less than 4 centimeters was around 100 percent. Over all the procedure has been proven successful as both a preventive surgery and as a last resort for those who have no other option to treat their diseases (Sutton, 2008).

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Although cryosurgery seems like the answer to treat diseases such as tumors, skin lesions, and various forms of cancer, there are disadvantages that have caused the procedure to not become a set in stone cure. As like all surgeries, different side effects may present themselves depending on the type of area being treated. According to recent studies treatment of cervical intraepithelial neoplasia can result in cramping, pain, or bleeding; treatment of skin cancer can lead to scarring or swelling; and treatment of bone tumors may lead to the destruction of nearby bone tissue (Pfenninger and Fowler, 2003). The biggest concern about this form of treatment is the uncertainty surrounding the long term effects. Even though cryosurgery has been around for decades, the procedure has been changed so many times that there has not been enough time for researchers to study the long term effects that could pursue from freezing skin lesions and diseased tissue at such low temperatures. Also, during the procedure physicians usually use imaging tests to locate and track the growth of the tumor; however, it is common for microscopic cancers to be missed when using a lower grade of imaging such as an ultrasound. One of the most devastating effects of cryosurgery is that over freezing may lead to damage of surrounding tissue and since the amount of liquid nitrogen cannot be monitored while performing the procedure, over freezing can easily occur. As cryosurgery continues to be researched a lot of the disadvantages will begin to vanish as the process is modified to lessen the risk of side effects and surgical failure.

One of the unique aspects of cryosurgery is that every procedure, no matter what area of the body, uses the same surgical instrument to administer the freezing. The original cryo probe was designed like a 2 milliliter disposal syringe that was made up of a copper nail which was filed and polished to the correct size and shape to fit the barrel and neck of a syringe that can be fitted onto an insulated luer mount. The design was meant to be easily maneuverable and light so that it can be used on all areas of the body. Over the years hundreds of cryo probe designs have been made, some more expensive than others because each one uses different materials in its makeup and different equipment to allow the device to run. Inexpensive cryo probes can easily be produced using a common dermatology tool, known as a carbon dioxide pencil, as it has a similar diameter to the syringe barrel needed to perform the cryosurgical procedure. However, the price of a cryo probe can go up as things such as insulation or refillable canisters are added into the design. One of the most important aspects of the cryo probe is that the syringe must be designed in such a way that can easily fit through the tissues that make up a specific portion of the body. Usually cryo probes for general surgery are thicker and smaller since tumors in the general portion of the body tend to be larger and the muscle tissue tends to be easier to retract out of the way. Yet, in areas where every nerve is critical, like the brain or spine, the instruments tend to get longer and thinner. Even with all the years that the cryo probe has been designed and modified the risk of leakage to healthy tissue still remain the biggest fear of both the patient and the surgeon (Pfenninger and Fowler 101).

Research Question

Can a set amount of liquid nitrogen be administered in such a way as to lessen the risk of harm to healthy tissue?

Methods

I began my experiment by obtaining six culture dishes with contained bacterial cultures and one empty culture dish that were given to me by Professor Josh Cannon. After obtaining my culture dishes, I began by picking one of them that contained bacterial culture found its volume. In order to find the volume of the culture I first found the volume of the empty culture dish by placing it in 1000 mL beaker filled with 200 mL of water and recording the new water level. Next, I subtracted the original water level from the new water level to solve for the volume of the empty culture dish. Then, I found the volume of an empty plastic sandwich baggie by placing it in a 1000 mL beaker filled with 200 mL of water and recording the new water level. Afterward I subtracted the original water level from the new water level to solve for the volume of the baggie. After that, I placed the culture dish that contained the bacterial sample in the plastic baggie and then placed the baggie and the culture dish into another 1000 mL beaker filled with 200 mL of water and recorded the water level change. Subsequently, I subtracted the volume of the empty culture dish from the new water level and then took that answer and subtracted the volume of the baggie from it, solving for the volume of the bacterial sample. I followed next by repeating the process of placing the filled culture dish into the plastic baggie and placing the entire baggie in the 1000 mL beaker to solve for each individual volume. In order to see all of my volume results please see table #1.

Once all of my volumes were solved for I moved onto solving for the density of each bacterial culture in each individual culture dish. In order to solve for the density I began first by massing out the empty culture dish using a weighing scale. Next I placed each filled culture dish onto the scale and subtracted the weight of the empty culture dish from the weight of the filled culture dish to find the mass of the bacterial sample. Please see table #2 for all of the masses of

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each culture dish. After having all of the masses of the different culture dishes solved for I went onto solving for the density by using the formula $\text{density} = \text{mass}/\text{volume}$. For each culture dish I plugged in the mass and divided them by the corresponding volume I had already solved for.

Please see table #3 for the final densities.

Since I had solved for the densities and the volumes of each culture dish I moved onto the more mathematical portion of my project. I first began by creating my own formula by modifying the formula typically used for dilution ($M_1V_1 = M_2V_2$). I choose this formula because it is used to lower the concentration of a substance and I knew that if I could lower the concentration of my bacterial culture I could shrink it. To begin modifying the equation, so that it contained all variables that I was able to find, I replaced M_1 (which stands for the morality of the bacterial sample) and M_2 (which stands for the morality of the liquid nitrogen) with the formula to solve for morality ($\text{morality} = \text{number of moles}/\text{volume}$). Next, when looking at my new equation, I replaced the number of moles on each side of the equation, with the equation to solve for number of moles ($\text{number of moles} = \text{mass}/\text{molecular mass}$). Following that, I simplified my equation by multiplying ($\text{mass}/\text{molecular mass}$) by ($1/\text{volume}$) on each side of the equation. Next, I replaced the volume on the bottom of the ($\text{mass}/(\text{molecular mass times volume})$) on each side of the equation with the equation for volume ($\text{volume} = \text{mass}/\text{density}$), causing my equation to look akin to ($\text{mass}/(\text{molecular mass} * (\text{mass}/\text{density}))$). Finally I simplified my equation by multiplying ($\text{mass}/1$) times ($\text{density}/(\text{molecular mass} * \text{mass})$) and crossed out like terms to get my final equation ($\text{density}/\text{molecular mass} * \text{volume}_1 = (\text{density}/\text{molecular mass}) * \text{volume}_2$ (see table five for the full dilution equation modification). Using the information I solved for during the first part of this experiment I plugged in each culture dishes density, its corresponding volume and the molecular mass (238.30 g/mol) for each, using the same molecular mass for each culture

dish because it is a constant number that is alike between them all, into my equation and solved for Volume 2, or the volume of liquid nitrogen. Once I had the volume of liquid nitrogen solved for I added the exact amount of liquid nitrogen to the glass pipit and injected the specific amount into the cell culture. After waiting for the liquid nitrogen bubbles to settle I recorded the area of the frozen cell culture (the white area) and the area of the leakage (the dark yellow area). I figured that the yellow area represented the leakage because it wasn't frozen by the time the liquid nitrogen has clumped together. After measuring both the area of the frozen liquid nitrogen and the area of the leaking liquid nitrogen I went on to find the percentage of leakage by adding the area of the frozen liquid nitrogen to the area of the leakage and putting the area of the leakage over the total area to find the percent of harmed tissue.

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Results

By using my modified dilution equation to find specific amounts of liquid nitrogen per culture size, I was able to produce a low risk of harm to surrounding healthy tissue. After finding the percentage of leakage compared to the combined area of both the leakage and the frozen zone I combined the percentages and divided by six (six culture dishes) to discover that the average percentage of leakage in my experiments was 7.5%, or in other words the leakage did not go past .1 centimeter away from the frozen area.

Conclusions

Based on the results from my experiments I was able to answer my question (Can a set amount of liquid nitrogen be administered in such a way as to lessen the risk of harm to healthy tissue?) with a yes. The results proved that I was able to lessen the chance that healthy tissue would be harmed. Although my experiment produced the results I wanted, I still would have

liked for have made some modifications in order to receive more accurate information. For starters I would have liked to have used some form of catch system that would have been able to tell me the exact amount of liquid nitrogen that leaked out of the cell culture, instead of just taking the area of the leakage. Also I would have liked to have tested different bacterial and maybe even cell cultures in order to test my experiment on a broader scale. If I were to continue on with this project I would like to explore the idea of designing a new cryo probe on which you could enter the specific amount of liquid nitrogen that you wanted to use to be administered. Finally, I would look into extending my project into freezing cancer cells in the blood for disease like leukemia. Over all, my project has been a stepping stone on which I hope to build more research and experimental designs until I find the cure for life's most deadly disease through mathematical modifications in cryosurgery.

References

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Appendices

Table #1

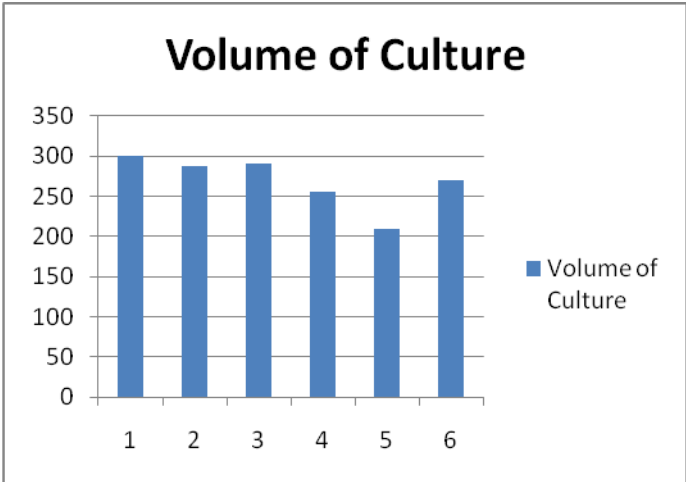


Table #2

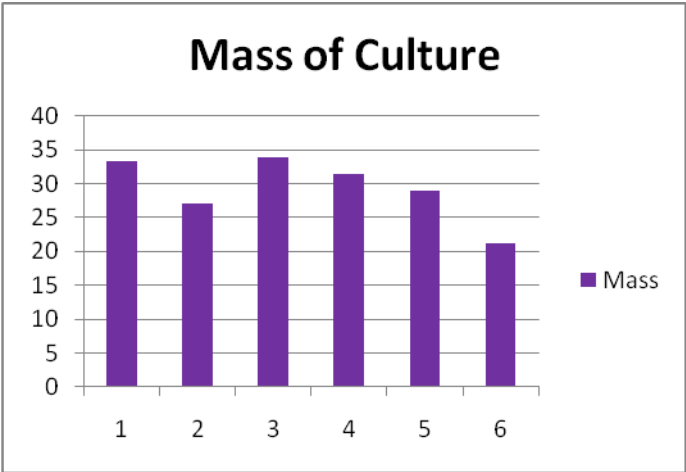


Table #3

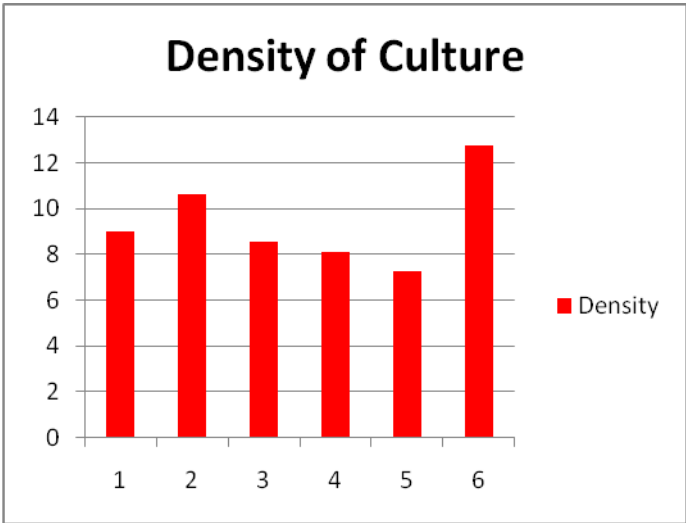


Table #4

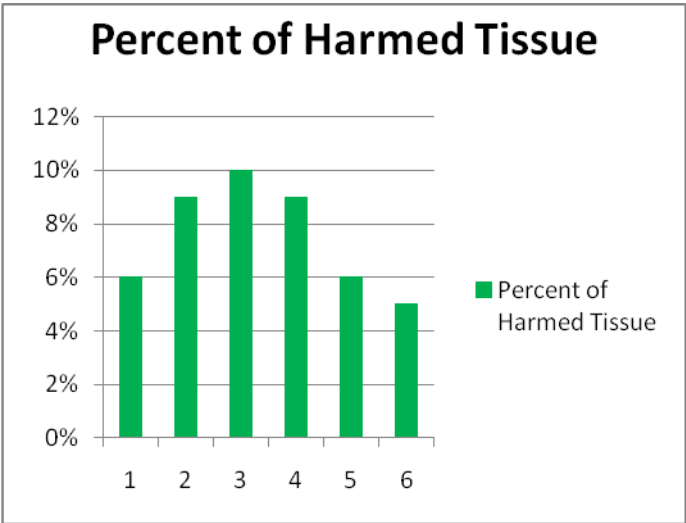


Table #5

$$M_1V_1=M_2V_2$$

$$\left(\frac{\text{number of moles}}{\text{volume}} \right) V_1 = \left(\frac{\text{number of moles}}{\text{volume}} \right) V_2$$

$$\left(\frac{\text{mass}}{\text{molecular mass}} \right) V_1 = \left(\frac{\text{mass}}{\text{molecular mass}} \right) V_2$$

$$\frac{\text{mass}}{\text{molecular mass}} * \frac{1}{\text{volume}} \quad \frac{\text{mass}}{\text{molecular mass}} * \frac{1}{\text{volume}}$$

$$\left(\frac{\text{molecular mass}}{\langle \text{volume} \rangle \langle \text{mass} \rangle} \right) V_1 = \left(\frac{\text{molecular mass}}{\langle \text{volume} \rangle \langle \text{mass} \rangle} \right) V_2$$

$$\left(\frac{\text{mass}}{\text{molecular mass} \langle \frac{\text{mass}}{\text{density}} \rangle} \right) V_1 = \left(\frac{\text{mass}}{\text{molecular mass} \langle \frac{\text{mass}}{\text{density}} \rangle} \right) V_2$$

$$\left(\frac{\text{mass}}{\frac{\text{molecular mass} * \text{mass}}{\text{density}}} \right) V_1 = \left(\frac{\text{mass}}{\frac{\text{molecular mass} * \text{mass}}{\text{density}}} \right) V_2$$

$$\left(\frac{\text{mass}}{1} * \frac{\text{density}}{\text{molecular mass} * \text{mass}} \right) V_1 = \left(\frac{\text{mass}}{1} * \frac{\text{density}}{\text{molecular mass} * \text{mass}} \right) V_2$$

$$\boxed{\left(\frac{\text{density}}{\text{molecular mass}} \right) V_1 = \left(\frac{\text{density}}{\text{molecular mass}} \right) V_2}$$