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Review Article

Nanotechnology Applications in Controlling Hemorrhage

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Abstract

Hemorrhage is defined as a profuse escape of blood from a ruptured blood vessel. This term is often associated with physical trauma and is responsible for 30-40% of trauma-related deaths with 33-56% of these occurring in the prehospital setting. Hemorrhagic shock is the second leading cause of preventable early deaths in injured civilian patients, and it is the number one cause of preventable death on the battlefield. The solution to this issue is achieving hemostasis in a timely manner. Hemostasis is the process that prevents blood loss following an injury. This process has three characteristics, the first is vasoconstriction, and the second is plug formation, which involves the collection of platelets to act as a physical plug to prevent blood from flowing. Last is coagulation, which is a cascade where a fibrin network is formed to act as a glue in holding the platelet plug in place. When an injury occurs, especially in the prehospital setting, a wound dressing is used to achieve hemostasis until a higher-level intervention can occur at a hospital. Currently, no out of hospital treatments that resolve the hemorrhage in non-compressible areas of the human body. Nanofibers can be used to mitigate issues that present with current treatment guidelines for bleeding in non-compressible hemorrhage. Previous studies have tested individual novel treatments for non-compressible hemorrhage and have tested against a control. This study aims to test eight of the novel interventions developed based on nanotechnology. This review compares these nano fiber systems using a porcine model with a splenic laceration in order to determine which is more effective in the management of non-compressible hemorrhage as measured by the time taken to achieve hemostasis and survivability.

Keywords: Nanotechnology applications; controlling hemorrhage; Nanofibers; Poly (γ-glutamic acid) hydrogels reinforced with bacterial cellulose nanofibers; Kappa carrageenan (κCA)-coated Starch/cellulose nanofiber; Injectable and super elastic nanofiber rectangle matrices ("peanuts"); nano spheres; PEI and Cholic Acid Injectable nano hemostats

Introduction

According to the Coalition for National Trauma Research, trauma is the number one cause of death for people ages 1-46 (Coalition for National Trauma Research). In the United States alone, trauma injuries account for over 150,000 deaths and over 3 million non-fatal injuries a year. Globally, trauma injuries cause over 5 million deaths in a year (Eastridge et al). Hemorrhage is responsible for 30-40% of trauma related deaths with 33-56% of these being in the prehospital setting. Hemorrhage is defined as a profuse escape of blood from a ruptured blood vessel. The causes of trauma related hemorrhage range from motor vehicle accidents, falls to conflict and weapon injuries (Injury Facts). Anything causing blunt force or penetrating injuries to a body can result in hemorrhage. With trauma injuries being a public health issue, there are several efforts made to prevent such injuries from occurring. Campaigns such as "Buckle-up" and DUI prevention while driving can reduce hemorrhagic accidents. Workplace safety programs, protective gear made

for civilian law enforcement and the military can provide better protection. Yet, despite best efforts, trauma injuries will always occur in both the civilian and military setting. In the civilian sector, motor vehicle crashes and falls account for the leading causes for preventable injury related death with hemorrhagic shock being the second, while hemorrhage from extremity wounds is the most common on the battlefield (Eastridge et al). To best manage and treat these patients, medical systems have developed algorithms and interventions to meet the specific needs of trauma patients. In the military, the prehospital algorithm is called tactical combat casualty care (TCCC) and in the civilian sector there are many different variations, such as advanced trauma lifesaving (ATLS) and prehospital trauma life support (PHTLS). Yet despite these carefully constructed algorithms, trauma injuries resulting in hemorrhage both prehospital and in hospital have a high mortality rate due to their unpredictable nature. With this, there is room for improvement with current trauma interventions to control bleeding to become more effective and with recent advances in nanotechnology this is possible. The solution to controlling and increasing the survivability of trauma related hemorrhage is achieving hemostasis as quickly as possible. Hemostasis is the process that prevents blood loss following an injury. This process has three characteristics, the first is vasoconstriction, the second is plug formation which involves the collection of platelets to act as a physical plug to prevent blood from flowing (Hangge et al). Last is coagulation which is a cascade where a fibrin network is formed to act as a glue in holding the platelet plug in place. When an injury occurs, especially in the prehospital setting, a wound dressing is used to achieve hemostasis until a higher-level intervention can occur at a hospital. There is a need for quick relief and stopping hemorrhagic blood flow in accidents. Presently there is no FDA approved system available in the market. There are three main types: arterial bleeding, venous bleeding, and capillary bleeding. Each type has its own causes, treatments, and considerations. Drastic blood loss, over 40% of blood volume loss, can cause shock, organ failure, and even death. The three different bleeding types differentiate by their origin. For the purpose of this paper, the interventions discussed focus on arterial bleeding. Arterial bleeding is the most severe and urgent type of bleed and is typically the main source of blood loss in a trauma incident. Due to the high pressure of an artery, when cut the injury pushes out blood with each pulse. This also proves challenging to control as the force of each heartbeat can disrupt the body's natural clotting process. The average time for someone to "bleed out" or to die as a result of blood loss is 2-5 minutes from an artery (Johnson). This rush for time calls for the need of more effective interventions to control hemorrhage.

Current Treatments

Hemorrhage can be divided into two categories: compressible and non-compressible hemorrhage. These categories are defined in relation to where the site of injury that causes blood loss occurs. Compressible hemorrhage occurs in an area of the body where compression or pressure can be used to control the bleeding. This would include the extremities, junctional areas and some parts of the neck. While non-compressible hemorrhage occurs in sites where compression cannot be used such as the "trunk" of the body which includes the chest and abdominal cavity. Current treatment of compressible hemorrhage include pressure applied above or on the site of injury to physically constrict vessels as to not let blood to pass and a wound dressing. Current means of applying pressure such as torniquets and pressure bandages have been shown to be widely effective in achieving hemostasis. Contrary to this, current pre- hospital treatment for non-compressible hemorrhage calls for oxygenation and fluid resuscitation to maintain blood volume until surgical intervention in a higher echelon of care can be reached however, at no point in current treatment guideline is bleeding stopped outside prior to surgical intervention (Kauvar et al). This demonstrates an urgent need for effective pre-hospital treatment for non-compressible hemorrhage which nanofibers can help resolve.

Nanofibers

Nanofibers; fibers with a diameter of 100 nanometers or less may be a solution to the improvement of achieving hemostasis in a timely and effective manner. Compared to commercially available dressings used, nanofibers produced via electrospinning have more elasticity, can cause less irritation to the injury because they are softer, and they have a higher specific surface area, which is the ratio of total surface area in relation to units of mass. Nanofibers can also more effectively carry drugs used to achieve hemostasis and enhance tissue repair while also having the ability to control their release (Sasmal et al).

Poly (γ-glutamic acid) hydrogels reinforced with bacterial cellulose nanofibers

Hydrogels are three-dimensional hydrophilic polymers that are structurally similar to biological tissues, which makes them favored in biomedical applications. Due to being composed of copious amounts of water, they tend to become brittle when swelling occurs via absorption. This would make a hydrogel dressing not suitable for hemorrhage where large amounts of blood needs to be absorbed. However, the advantage to using hydrogels is that they maintain a moist environment to promote wound healing and mitigate further issues and damage caused by tissue dehydration and cell death. As a way to enhance, the mechanical strength and overall mechanical stability of a hydrogel dressing scientists tested the use of bacterial cellulose nanofibers to reinforce the dressings. Poly (γ-glutamic acid) hydrogels were selected because they are highly biocompatible and biodegradable. Poly (γ-glutamic acid) is made via microbial fermentation and are particularly useful because the carboxyl groups on its side changes can be used as binding sites for drugs to better achieve hemostasis due to increased drug absorption. Bacterial cellulose nanofibers were selected as the reinforcement component because of its high crystallinity, high purity, high hygro-scopicity, and 3D structure. The reinforced hydrogels were made via a one-pot synthesis to improve the efficiency of the reaction where poly (γ-glutamic acid) was crosslinked in a bacterial cellulose nanofiber suspension. Doing so allowed for increased energy dispersion amongst hydrogen bonds thereby increasing better strength in the hydrogels. When compared to the traditional, non- reinforced hydrogels , the bacterial cellulose nanofiber reinforced hydrogels showed an x8.16 increase in tensile strength which would improve issues of absorption in hemorrhage applications. Allowing more blood to be absorbed in the dressing can help promote hemostasis by pulling blood away from the site of injury so a platelet plug can be formed and maintained by a fibrin network. In cytotoxicity tests, the reinforced hydrogels demonstrated good cytocompatibility making it suitable for biomedical applications (Dou et al).

Kappa carrageenan (κCA)-coated Starch/cellulose nanofiber

Aiming to fix the same issue with the structural integrity of hydrogel dressings, another group of scientists developed Kappa carrageenan (κCA)-coated Starch/cellulose nanofiber hydrogel and test it in relation to a cellulose nanofiber hydrogel similar to the one described above. Carrageenan is a linear polysaccharide extracted from red seaweed that is used in several industries to thicken and stabilize products. It was found that by coating the nanofiber with k-carrageenan the hydrogel doubled in mechanical strength in comparison to the non-coated cellulose nanofiber hydrogel with strength increasing as k-carrageenan content increased. It was also found that the degradation rate of the coated nanofiber hydrogels was cut in half in comparison to the non-coated. When tested in applications related to hemorrhaging, clotting tests showed no improvement in clotting ability in relation to the non-coated nanofiber hydrogels. So, while there is no improvement in clotting ability, benefits of the coated hydrogels come from the improved mechanical strength which can promote absorbability in hemorrhage applications and aid in the integrity of this as an intervention in the pre-hospital setting (Tavkoli et al).

Porous Electrospun Starch Rich PCL Nanofibers

Starch has been used for hemostatic applications due to its amorphous nature and its ability to enhance or contribute to the blood coagulation pathway due to the presence of phospholipids. By dehydrating blood, starch causes the formation of a solid that acts as a barrier, which can support and enhance the clotting cascade and lead to the reduction of blood loss in a timely fashion. Current starch hemostats are found in the form of powder and are difficult to use when there is a large volume of blood present prior to deploying the powder. The powder form can be hard to direct at the site of injury and not target the source of bleeding due to the inability to guide or direct the powder to the injured vessel. By electrospinning starch into a fiber, these deficiencies can be overcome. In 2018, two researchers from Anna University in Chennai, India tested electro spun starch rich polycaprolactone blend nanofibers and their application to severe hemorrhage. The nanofibers were created with varying ratios of PCL to starch however, it was found that a 1:1 ratio crested a uniform bead free fiber, and this composition was used in hemorrhage application testing. In comparison to a PCL fiber mat that was not blended with starch, the blended fiber mat showed a 240% increase in swelling. In blood clotting tests using the modified Lee and White method where a vein was punctured and 1 ml blood was deposited into a tube where a 1x1 cm fiber matt

resided, the PCL-Starch nanofibers showed a 156 second clotting time which was less that all other mats tested as well as the control of the standard starch powder used. With this, the PCL-starch blended nanofibers showed improved hemostatic potential and achieved hemostasis quicker than conventional methods (Dev et al).

Layered Nanofiber Sponge

As mentioned previously, current wound dressings exhibit structural deficiencies which can prevent the achievement of hemostasis. In 2019, researchers tested a 3-D chitosan nanofiber layer sponge and its applications in promoting blood coagulation and wound healing. The chitosan and polyvinyl alcohol blend was electrospun to create a non-beaded nanofiber that was then formed in a layered sponge. The layered structure increased the surface interaction and adhesion between the sponge and the blood cells at the site of injury. This increase in interaction was shown to accelerate hemostasis. The sponge also demonstrated high elasticity, permeability to oxygen and a large absorption capability, all which are promoters of wound healing. In mice models, the sponge showed to be highly compressible and effective in tamponading a wound that would be characterized as deep in nature. In the same mice model, the sponge showed a reduction in scar formation which is a prime indicator that the sponge provides an ideal environment for wound and tissue healing (Li et al).

Tranexamic acid-loaded chitosan electrospun nanofibers

Tranexamic acid (TXA) is a drug used to reduce bleeding by inhibiting the breakdown of blood clots when given in an appropriate time frame. It prevents plasminogen from being converted into activated plasmin. This leads to less fibrinolysis, prevents clots from being broken down and aids in quickly forming more stable clots. Also, while the body may form clots at the site of injury, if profuse bleeding is occurring, the clots can be dislodged and this is another reason why the formation of more stable clots are necessary. Hemostatic patches made of chitosan nanofibers with encapsulated TXA were formulated. Two variations of the nanofibers were made, a 1:1 and a 3:2 ratio of polyvinyl alcohol and chitosan. In clotting time tests, the 1:1 showed an average 167 second clotting time while the 3:2 showed an average 210 second clotting time. However, both showed a significantly faster clotting time compared to the control without any intervention. By delivering the TXA with the mechanical barrier of the nanofibers as opposed to the traditional intravenous delivery, additional mechanical occlusion of the injury assisted in achieving hemostasis. Additionally, by directly delivering the TXA straight to the site of injury, a lower concentration and dose of it was found to be therapeutic in comparison to conventional application standards (Sasmal et al).

Liposomes loaded with TXA

Another study using the same idea sought to test the use of liposomes as a delivery model for tranexamic acid. In order to do this, liposomal vesicles were coated with *cyclo-CNPRGDY(OEt)RC* peptide (Bertram et al). This peptide has a high affinity for active platelets in trauma associated clots and then encapsulates the vesicles with TXA. In the study, the loaded liposomes were tested in vitro in rat blood and then in vivo in a liver trauma model also in rats. This was then compared against TXA loaded nanoparticles without the peptide coating, TXA alone and normal saline. When tested in vitro, the coated and loaded nanoparticles were able to resist lysis in rat blood that contained TPA, a usual antagonist to TXA. Then, in vivo the loaded and coated nanoparticles were able to significantly reduce blood loss in the liver trauma model and improve survivability. In postmortem analysis of the rat tissue also showed general systemic safety (Girish et al).

Fibrin coated Albumin nanoparticles

Thrombocytopenia is defined as a condition where there is a low blood platelet count. Platelets are blood cells that aid in the clotting process to stop bleeding and ultimately achieve hemostasis, they do this by traveling to the site of injury and forming plugs by aggregating together at the site of an injured blood vessel (Mayo Clinic). Thrombocytopenia is a disorder that typically coincides with those with autoimmune disorders or those who are receiving chemotherapy. Lack of these platelets can cause life-threatening bleeding. While thrombocytopenia is not typically used to describe trauma patients, low platelet counts are something shared between the

two. Due to high volumes of blood loss and possible dilution using prehospital measures of volume replacement such as normal saline or lactated ringers, platelet counts are found to be low in patients after trauma. In a study done focusing on severe thrombocytopenia, a platelet substitute was developed called synthocytes that are made up of albumin microcapsules with fibrinogen attached to the surface (Hobisch-Hagen et al). As one of the most abundant proteins in blood plasma, serum albumin helps to keep fluids within blood vessels instead of escaping into tissue. It is also commonly used in the form of a transfusion in patients presenting with shock to remove fluid from tissues and back into the bloodstream. Albumin serves as a carrier for antithrombin and heparin cofactor (Paar et al). Antithrombin regulates the activity of thrombin to only be activated unless needed and heparin cofactor aids in the anticlotting mechanism of heparin (Moore et al). When the albumin nanoparticles with attached fibrinogen were delivered intravenously into a rabbit trauma model, it reduced the bleeding time compared to the control of saline. While studied with the focus of thrombocytopenia, these synthocytes could also prove useful and have similar effects in trauma patients to reduce blood loss by controlling fluid loss and bleeding time (Levi et al).

Superhydrophobic Hemostatic Carbon Nanofiber composites

Cotton gauze is a standard material used as a wound dressing in hemorrhage due to its absorption capacity. However, blood that is absorbed in the gauze turns into a solid and adheres to the site of injury. This then requires peeling of the material when going to assess and further sites of hemorrhage. This peeling can dislodge clots that occluded hemorrhage in the first place and cause a recurrence of blood loss. By creating a superhydrophobic surface with immobilized carbon nanofibers researchers found that minimal interface interaction was formed between the clot at the site of injury and the dressing. In rat models, this significantly reduced the undesired effects caused by adhesion in cotton gauze models. It was also found that carbon nanofibers promoted fibrin growth which helps stabilize and form clots. Due to this, in clotting tests, the composites showed a reduced clotting time in comparison to a cotton gauze model and showed a reduction in blood loss (Li et al).

Injectable and superelastic nanofiber rectangle matrices ("peanuts")

As mentioned before, Current prehospital treatment guidelines for internal non-compressible hemorrhage call for oxygenation and fluid resuscitation to maintain blood volume until surgical intervention in a higher echelon of care can be reached however, at no point is bleeding stopped. the development of injectable electrospun polycaprolactone nanofiber mats or "nanofiber peanuts" can resolve this issue. To form them, PCL beads are dissolved and spun to make rectangular mats that are then vacuumed and freeze-dried which would expand upon contact with a liquid such as blood. The nanofiber peanuts were then tested against currently available hemostatic technologies in the categories of water absorption, clotting ability and time, and hemostatic ability. In the tests, the nanofiber peanuts showed the highest capacity of water absorption, fastest clotting time with the most physiological similar pH. The most promising demonstration of in-vivo hemostatic abilities of the peanuts was the ability to maintain a physiologically appropriate mean arterial blood pressure with minimal blood loss in a porcine liver injury model. Past research struggled to construct an effective hemostatic material suitable for injection in areas of non-compressible hemorrhage, specifically the torso. The nanofiber peanuts overcome this limit as they are compressed pellets that can be injected into the torso via a syringe and expand within seconds to promote hemostasis via pressure. In addition to this, the use of a hemostatic agent such as thrombin was tested in conjunction with the peanuts and showed promising results of platelet adhesion and hemostasis (Chen et al).

Injectable antibacterial cellulose nanofiber/chitosan aerogel

Similar to the injectable peanuts, an injectable antibacterial aerogel was formulated to mitigate issues with non-compressible hemorrhage. In the same way as the peanuts, the aerogels effectively tamponade hemorrhage in non-compressible areas but had an added benefit of antibacterial properties. This was made with a cellulose nanofiber and a modified chitosan where carboxyl groups were pre oxidized. Once formulated, the result was an aerogel nanofiber sheet. An issue with current wound dressings is a probability of infection. This aerogel showed promising antibacterial properties as well as a high absorption capacity, high mechanical strength as well as good biocompatibility (Fan et al).

Nanospheres

Recombinant activated factor VII is a hemostatic agent made to mimic the effects of factor VII (Mayo Clinic). Factor VII is a naturally occurring protease in the body that serves to start the process of thrombin generation, fibrin deposition and platelet activation within the clotting cascade (Rajpurkar et al). However when using recombinant factor 7 there are risks of immunogenic and thromboembolic complications (Bulto et al). To advance this technology and mitigate risk, researchers developed a synthetic platelet based on Arg-Gly-Asp functionalized nanoparticles. These hemostatic nanospheres were made of polymers such as poly-lacticglycolic acid–poly-L-lysine and polyethylene glycol. The researchers wanted to develop a product to target internal injuries and bleeding while being stable at room temperature and easy to use. When studies compared the nanospheres delivered IV and recombinant factor VIIa the nanospheres were able to reduce the bleeding time in a rat model inflicted with major trauma by half. Further analysis also showed that the nanospheres cleared the body within 24 hours when given at 20mg/ml and showed no complications one week post infusion. This would be ideal for those with injuries sustained from blunt force trauma. Studying this idea further, researchers took those same nanospheres and tested it on a rat blast trauma model. In the model the mice where subject to blast overpressures of 15, 20 and 25 psi and then received a dose of nanospheres via a retro-orbital injection. It was shown that the hemostatic nanoparticles increased survivability of the rats by 35% in the 20 psi blast from 60% to 95%. However, there was no significant difference in survivability in the other pressures. At the 15 psi without treatment 100% of rats survived rendering the hemostatic nanoparticles not needed to improve 1 hour post blast survivability. At the 25 psi, without treatment only 10% of rats survived and the percent did not significantly increase with the administration of a hemostatic nanosphere (Lashof-Sullivan et al).

PEI and Cholic Acid Injectable nano hemostats

In a study, nanoparticles were generated through the self-assembly of polyethyleneimine (PEI) facilitated by cholic acid. The formation of the nanoparticles was driven by interactions between cholic acid and PEI, including electrostatic, hydrogen bonding, and hydrophobic forces. In vitro studies indicated that the assembled nanoparticles effectively caused platelets to aggregate and activate. Applying an aqueous solution containing nanoparticles was shown to decrease the time to achieve hemostasis in the rat model. Injuries tested on include mouse tail lacerations, rat liver bleeding, and rabbit femoral artery bleeding. Furthermore, intravenous injection of the positively charged nanoparticles prevented bleeding in the rat femoral artery by targeting the injury site through fibrinogen-mediated channels (Cheng et al).

Conclusion

In conclusion, with uncontrolled hemorrhage accounting for 40% of deaths resulting from trauma and being the number one cause of death in combat current treatment modalities have significant grounds to cover in decreasing blood loss and reaching hemostasis in prehospital settings. There are many effective measures for controlling hemorrhage in compressible areas such as the extremities. However current interventions lack when discussing controlling hemorrhage in non-compressible areas within the prehospital setting. Aside from fluid replacement from crystalloids or blood which most providers pre-hospital do not always have, there are few current treatments to actually stop the bleed when it cannot be compressed. As discussed in this paper, nanotechnology can help bridge the gap in this area of trauma care. By providing safe and effective options for various intravenous or injectable hemostats, prehospital providers would have the ability to not just manage the symptoms and changes of a patient with internal bleeding, but be able to effectively stop the bleed and have the potential to stabilize the patient before transferring care. In trauma medicine, there is a concept called the golden hour. The golden hour is the idea that if severe trauma patients do not reach definitive care such as a hospital within an hour post injury, the mortality significantly increases (Alarhayem et al). When considering the time for first responders to reach a scene, possible delays in extraction and transport time to an appropriate trauma center, this hour can be very slim. This not only comments on the severeness of the patients' injuries but draws light to the lack of care prehospital providers are able to give with current interventions and treatments. Using some of the nanomedicine discussed in this paper, this golden hour could possibly be extended by giving prehospital providers the tools to better treat the patient.

Future Trends

There are many directions as to where this research can go and what advancements can be made. Further research can be done as to how to make the technology discussed above more effective and faster at stabilizing patients. Also, more work can be done as to how to make these products cheaper and more shelf stable in order to make them more accessible to prehospital providers such as EMS systems which are historically underfunded. Advances such as those discussed have the potential to revolutionize the trauma and EMS industry however it would be deemed useless if it was not able to be acquired by those who would have the most potential to use it. Another possible avenue for advancement is studying different routes of administration for the technology and its impact on effectiveness. While intravenous infusion is often considered to be the best route of administration in terms of bioavailability and quickness of onset, in many trauma cases, IV access can be challenging. When major blood loss occurs, veins are difficult to access combined with any potential physical injuries preventing access such as amputations and burns. Routes such as intraosseous access, endotracheal access and even intramuscular access should all be explored when considering the demographic of the patient these technologies are meant to be used in. When focusing on just the nanofibers discussed, things such as blood saturation and volume should be looked at. At what volume of blood saturation of the fiber or sponge would it be considered ineffective and the hemostatic agents no longer able to function. Finally drug to drug interactions given the compounds used should also be evaluated. Most of the studies discussed only tested the nanomedicine's ability to stop bleeding in an isolated animal model. However, in a real trauma there are several drugs being used within a short amount of time causing the potential for many drug interactions not even considering possible medications the patient could be on prior to an injury.

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