Investigating a Hybrid Nanoparticle System for Deep Vein Thrombosis Treatment and Detection

Introduction

It has been estimated that deep vein thrombosis (DVT) affects nearly two million people in the United States (Wadajkar, 2013). Approximately 60,000 to 100,000 Americans will die due to illness relating to venous thromboembolism. DVT is a serious threat because many of the symptoms, including swelling, pain, and discoloration, are often overlooked, allowing mortality to be completely undetected. Typically, 10% to 30% of patients will die within one month of diagnosis.

Deep vein thrombosis describes a blood clot formed in a vein deep inside a person's body. Areas prone to this include the lower leg, thigh, and pelvis, although thrombosis can also occur in other places in the body as well Conventional treatments for DVT include basic lifestyle modifications, such as monitoring vitamin K intake, exercising, and applying mechanical compression. Other treatments can involve more serious measures including anticoagulant therapy, inferior vena cava filter, or thrombolysis. However, these treatment options often have side effects ranging from improper clot clearance to an increased risk of hemorrhage occurrence, the escape of blood from a ruptured blood vessel.

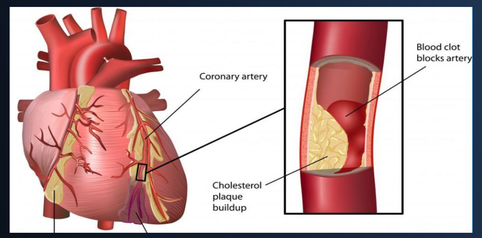

Figure 1. Illustration of a thrombus formation within the major artery of the heart. (Disease and Conditions, 2018)

This study is an evaluation of whether a multifunctional nanoparticle system can eliminate blood clots more efficiently in the human body and also assist in the detection of early thrombus formation. The focus is design for a hybrid nanoparticle system with the addition of PPACK that aids in both the detection and treatment of DVT through the identification of P-selectin is absent.

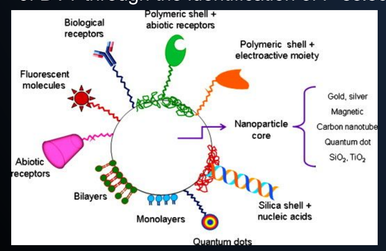

Figure 2. Structure and composition of a multifunctional nanoparticles (MFNP). Nanoparticle core can be doped with different nanoparticle and/or dye (Simón de Dios, 2010)

Purpose

The purpose of this study is to determine whether PPACK can be added to the nanoparticles cores as a way to increase efficiency of thrombin removal. Furthermore, this study is an evaluation whether sPsel can be a valid biomarker for locating acute thrombosis formation within the body.

Hypothesis

Alternate: PPACK Nanoparticles can be used to increase efficiency of thrombin removal as well as sPsel be used as a valid biomarker for acute thrombosis formation.

Null: Due to toxicity and inaccuracy, PPACK nanoparticles and soluble P-selectin cannot be applied for deep vein thrombosis treatment and detection.

Methods

The research design was conducted via secondary data analysis. A few sources used to retrieve information regarding this topic that were capable of reaching were Ebscohost, CSUCI's library databases, or PubMed. Most studies were taken between the years 2006-2017. Through systematic review, different designs of nanoparticles specific for DVT were reviewed and various biomarkers were studied to understand the effectiveness.

Data was obtained by analyzing studies testing the occlusion time of three different forms of treatment. The efficiency of PPACK NPs was determined by comparing the delayed occlusion time in vivo. Mice were used through all studies and were given each form of treatment option in separate groups. Carotid artery experiments were conducted either through acute photochemical injury or laser injury to assess effects of PPACK NPs.

Evaluation of the accuracy on P-selectin predicting thrombus formation was conducted by comparing patients with DVT and patients without DVT. Data also included other biomarkers for diagnosing DVT, including the most common clinical marker, D-dimer. Differences in pre and post P-selectin concentrations were measured to determine the biomarker accuracy. Unit conversions were applied to all necessary studies to allow proper comparisons. Statistical analysis was performed t-test using two tail distribution with $p < 0.05$ considered statistically significant.

Results

A total of 2798 patients were analyzed in 12 studies containing both a negative DVT group and positive DVT group. Each table displays a common DVT biomarker Concentrations of sPsel were recorded as well as the Wells score, CRP, and D-dimer test being interpreted in both negative and positive DVT groups. A difference in these two values allowed for an evaluation of the accuracy on these biomarkers. P values for sPsel, D-dimer, C-reactive protein, and Wells Score were determined to be 0.034, 0.153, 0.723, and 0.086 respectively. Average concentrations for the negative DVT groups include sPsel: 37.731 (ng/mL), D-dimer: 2565.983 (ng/mL), and C-reactive protein: 7.567 (µg/mL). Negative DVT through Wells score had an average of 1.878. The average concentrations for positive DVT are sPsel: 61.492 (ng/mL), D-dimer: 4629.516 (ng/mL), and C-reactive protein: 9.665 (µg/mL).

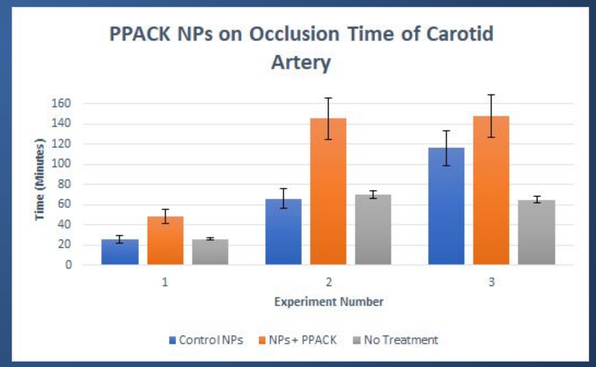

Figure 5A. Comparison on the effectiveness of various treatments on occlusion time. (Myerson et al., 2012 & Palekar et al., 2017).

Biomarker (ng/mL)	Negative for DVT (95% CI)	Positive for DVT (95% CI)	Study Analyzed
Soluble P-selectin	40.5	51.8	Gremmel et al. (2011)
Soluble P-selectin	53.4	87.3	Ramacciotti et al. (2011)
Soluble P-selectin	54.5	77.2	Vandy et al. (2014)
Soluble P-selectin	50.0	77.4	Angelini et al. (2014)
Soluble P-selectin	14.18	93.06	Saadeldin et al. (2018)
Soluble P-selectin	48.9	31.6	Jungbauer et al. (2007)
Soluble P-selectin	42.1	45.9	Ay et al. 2007)
Soluble P-selectin	9.16	51.46	Hameed et al. (2017)
Soluble P-selectin	11.37	12.5	Entezari-Maleki et al. (2013)
Soluble P-selectin	53.2	86.70	Sood et al (2012)
Standard Deviation	18.66	26.9	

Table 2a. Soluble P-selectin being used as a biomarker for determining thrombus formation. Concentrations were measured in vivo comparing groups positive for DVT and control group negative for DVT.

Discussion

PPACK is beneficial when it is covalently secured on the surface of perfluorocarbon-core nanoparticle structures. When attached to nanoparticles, they have a kinetic advantage rather than their free roam state on thrombin activity, allowing PPACK NPs to present thrombin-inhibiting surfaces to early thrombi formation.

Compared to all previous biomarkers, sPsel has demonstrated the most consistent correlation through the studies analyzed on acute thrombus formation. One cause of sPsel's correlation with DVT is its role in platelet related activation. Procoagulant microparticles form due to the interaction it has with P-selectin glycoprotein ligand 1 (PSGL-1): main counter receptor on leukocytes. This interaction increases expression of tissue factor, the main activator of coagulation in vivo, which is physically separated by the endothelium. This increase in expression essentially causes a coagulation cascade as sPsel increases surface-dependent thrombin generation on monocytes and induces phospholipid (phosphatidylserine) which plays a key role in cell signaling

Conclusion

Nanotechnology offers a promising solution as it has an advantage compared to other conventional treatments for DVT because they can work at the molecular level. Nanoparticles with the addition of PPACK can be used a treatment option for thrombin removal. Furthermore, sPsel can be a valid biomarker to locate acute thrombus formation

Further Work

The major risk of implementing nanoparticles into the medical field is due to DEPs and UFPs. Nanoparticles have the capability of generating pro-inflammation and may induce oxidative stress, possible factors which could lead to respiratory pathology. More research should look into the risk of nanoparticle toxicity when inserted into human tissue. A method of dealing with this issue can be using an oxidative stress paradigm as screening for nanomaterial toxicity as it can test for cellular injury responses.

References

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