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Innovative Dressing for Invasive Bloodstream Access Sites

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Abstract

Goal: The goal of our work was to develop a new Nano fiber-based membrane dressing for covering invasive access to the bloodstream sites that would prolong the time interval between catheters changes in patients with central or peripheral venous catheters as well as increasing dressing change intervals. Increasing both intervals would reduce the incidence of nosocomial infections and increase the quality of patient care significantly.

Material and methodology: Between 2014-2017, we worked on a project supported by the Technology Agency of the Czech Republic (TA CR) to develop a special dressing based on Nano fibers activated by a photosensitizer that facilitated the formation of singlet oxygen, which has strong disinfectant effects and does not contribute to antibiotic resistance. The antimicrobial effects of currently available dressing materials are associated with antibiotics or disinfectants (e.g., chlorhexidine). In 2014, we started to prepare and test suitable polymers. In 2015, we developed a dressing and demonstrated, using the triiodi de test, that it produced a significant amount of singlet oxygen after light exposure. We further confirmed that the new dressing had significant bactericidal effects. Between 2016–2017, *in vitro* tests were conducted using four typical bacterial strains found in hospitals, and applying singlet oxygen-inducing lighting for various lengths of time. Additionally, we performed *in vivo* testing of the nanofiber membrane relative to skin sensitization tests, irritation tests, phototoxicity, and penetration tests on laboratory mice and human skin models.

Results: Our Nano fiber dressing proved innovative in its use of the unique properties of Nano fiber materials combined with singlet oxygen. The seven μm thick membrane proved to be the most effective, and an LED 410–420 nm lamp operating for 10 minutes at a distance of 10 cm appears to be the most suitable light source for inducing singlet oxygen. *In vivo* tests showed that the Nano fiber membrane supplemented with TPP does not irritate skin, does not sensitize, is not phototoxic, and it does not penetrate the skin.

Conclusion: The Nano fiber dressing material supplemented with TPP has the prerequisites for use as medical equipment in clinical practice. The prototype of this material is registered as a utility model at the Industrial Property Office.

Keywords: Nano fibers; Vascular access; Dressing materials; Bactericidal effects

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Abbrivations: TPP: Tetra Phenyl Porphyrin; TA: Technology Agency; CR: Czech Republic; CDC: Centers for Disease Control and Prevention; INS: Infusion Nurses Society

Introduction

Nano fibers are starting to influence almost every field of human activity. They can repel dust, purify water and can be used to make clothes. They also have applications in medicine, both superficially, and now it appears, inside the human body as well. Our project "Dressing for Invasive Access to the Bloodstream" was to develop new nanoparticle-based dressings for use on invasive bloodstream access sites. The goal was to use the dressing to extend the interval between catheters changes in patients with established central or peripheral venous catheters. Prolonging the change interval would contribute to a reduction in nosocomial infections and a significant increase in the quality of care. As part of the project, nurses, physicians, chemists, and laboratory staff worked to develop special nanofiber-based dressings. Such dressings are activated by a photosensitizer that facilitates the formation of singlet oxygen. Singlet oxygen is a strong disinfectant and does not lead to antibiotic resistance. The production of Nano fibers was carried out by the Technical University Liberec, Czech Republic [1]. The innovative nature of our solution lies with the unique properties of Nano fiber materials in combination with singlet oxygen. The new Nano fiber dressing compares favorably to available dressing materials whose antimicrobial effects depend on antibiotics or disinfectants (e.g., Chlorhexidine).

Background

Dressings for peripheral and central venous catheters - current state

Nosocomial infections are a common complication of healthcare and have a number of negative consequences. These include increased morbidity and mortality, deterioration in the quality of life of patients, prolonged hospitalization, and increased health care costs. Each introduction of an intravascular catheter carries an infection risk because it punctures the patient's skin. Microorganisms, such as coagulase-negative Staphylococcus are common causes of catheter infections. Other potential pathogens, e.g., Staphylococcus epidermidis, gram-positive bacteria such as Staphylococcus aureus, gram-negative rods such as Pseudomonas aeruginoza, Serratia marcescens, Burkholderia cepacia, and yeast such as Candida, are all normal components of the natural micro flora of the skin and mucous membranes and can get into the body exogenously, either extraluminally or intraluminally. Extraluminally means that microorganisms migrate from the skin along the catheter into the bloodstream; the source of the microorganisms can be the catheter cover or the patient's skin microbial flora. Most of these infections occur within the first week after the catheter is introduced. Intraluminal sources of infection are generally associated with hospital staff [2-5].

In patients with a peripheral venous catheter, we most often encounter local inflammations, especially phlebitis. The cause of phlebitis can be bacterial contamination, mechanical, or chemical irritation of the vessel. Mechanical phlebitis arises when the catheter is poorly fixed and irritates the tunica intima of the vessel [2,6,7]. Sepsis is more likely to occur in patients with central venous catheters, with the short-term central venous catheters used in intensive care being the main culprit [2,3,8].

Factors influencing the formation of infections associated with vascular access unambiguously include the dressing material used [2,3,9].

Types of cover materials

Injection site coverage plays an important role in the prevention of infections associated with vascular access. Dressing material protects the injection site from the external environment, microorganisms, and minimizes movement of the catheter to prevent dislocation, infiltration, and extravasation. Each micro-movement of the cannula leads to irritation of the venous wall and subsequent signs of inflammation. Ideally, catheter dressings should be sterile, easy to use, removable, and patient-friendly [7,9]. In routine practice, for central venous catheters, nurses usually use a transparent foil dressing or a textile-film dressing with chlorhexidine. To cover peripheral access sites, nurses often use a textile dressing or a textile-film dressing without chlorhexidine. For nurses, the advantage of transparent foil dressings is that they are transparent and waterproof. The disadvantages are they are non-absorptive, the skin under the bandage sweats, which can reduce adhesion, and the dressing is not stable on high friction areas and active patients. Transparent dressings usually need to be changed every 2–7 days. For nurses, the advantages of textile dressings are their absorbency, adhesion, and they are less irritating to the skin, but since they are opaque, they must be changed daily or according to hospital standards. When removing the dressing, catheter micro-movements occur, which causes vessel irritation and increases the risk of cannula contamination or complete catheter dislocation. Moreover, irritation and injury to the skin can occur when the dressing is removed, making the

area more susceptible to colonization by pathogenic microorganisms. Nurses often use a textile-film dressing with Chlorhexidine to cover peripheral venous catheters. Nurses appreciate that it combines the benefits of a transparent and textile cover. They can see the injection site, and the dressing does not need to be changed daily. Therefore, skin irritation is decreased. The best dressing characteristics are transparency, waterproof but breathable, with good adhesion but easily and comfortably removable [10-14].

Criteria for the development of a dressing from a nursing perspective

a. The dressing material must meet the requirements mentioned above.

b. The dressing material must be fully functional, not just in terms of a catheter dressing, but also fixation.

c. Ideally, the coated microfiber dressing, which will act as a disinfectant, can be left in place the entire time the dressing is needed.

d. According to the current guidelines of the Centers for Disease Control and Prevention (CDC) and the Infusion Nurses Society (INS), the frequency of dressing changes is not dependent on the dressing material (i.e., whether the dressing is transparent or not); this applies to peripheral venous catheters but not to central venous catheters [15,16].

e. Using a pilot survey in hospitals, we identified local hospital standards in the Czech Republic for peripheral venous catheter dressing changes (39). There was some inconsistency in the protocols. In 67% of the cases, the frequency of dressing changes was 72 hours; the INS recommendation, on the other hand, was 5–7 days, unless otherwise indicated.

Method of Laboratory Solution

The laboratory part of the project included the preparation of suitable polymers, electrostatic spinning of polymer solutions, and testing under laboratory conditions. We decided to improve upon the current Tegaderm film dressing by adding a hydrophilic polyurethane nanofiber membrane supplemented with a photosensitizer. The presence of the photosensitizer causes the formation of strongly bactericidal and virucidal singlet oxygen under normal white light (natural or artificial). Singlet oxygen has a relatively short life span (≈ 3 μs), so it only oxidizes objects in the immediate vicinity of the membrane (up to about 200 nm). Of great importance is that there is no known acquired resistance to the anti-microbial effects of singlet oxygen. The positive characteristics of the Tegaderm dressing are its transparency, strength, good adhesion to the skin without allergic effects, and partial breathability. The vapor permeability of the polyurethane membrane is approximately 700 g / (m^2 × 24 hours), which is about three times the normal amount of water vapor produced by healthy skin. The disadvantage of Tegaderm is its hydrophobic surface that prevents the absorption of any exudate from the cannula insertion site. Therefore, the fluid accumulates under the dressing film. Some Tegaderm products also contain chlorhexidine-impregnated gel patches that are gradually released into the cannula and its surroundings to prevent catheter infections. The disadvantage of this gel is that it is hydrophobic, and the presence of chlorhexidine in the wound is not always desirable.

Selection of a suitable polymer, testing under laboratory conditions, and electrostatic spinning of polymeric materials

We selected Tecophilic HP-60D-60 polyurethane as the most suitable material for the preparation of a nanofiber cannula dressing for the following reasons:

a. The polymer has been tested for use in medical applications;

b. It is capable of absorbing up to 100%, of its dry weight, of water;

c. It shows good permeability for gases, especially oxygen.

The most suitable photosensitizer was water-insoluble non-polar 5,10,15,20-meso-tetraphenylporphyrin (TPP). It provides a relatively high quantum yield of singlet oxygen and is subject to very slow photo degradation. Photo production of singlet oxygen was verified using an in vitro iodine test method (41), with positive results. This method also verified the ability of singlet oxygen to migrate from the Nano fiber layer to the surrounding medium. After supplementing the Nano fiber membrane with TPP photosensitizer, production of singlet oxygen was demonstrated. In the next phase of the research, we addressed the issue of membrane thickness. The membrane needed to be thick enough to produce enough singlet oxygen to have good bactericidal efficacy, while avoiding adverse effects on the skin. The entire system could, therefore, be easily applied and easily removed after a determined time for removal and to keep the desirable characteristics of cannula dressing.

Solving the thickness and fixation issues for the nano fiber layer

We prepared several variants of membranes with a nanofiber thickness of 7, 14, 24, and 35 μm. We measured the production of singlet oxygen from these membranes,

and we found that all membranes had sufficiently high production. With regard to the optimum thickness of the membrane, we were therefore guided by its mechanical characteristics, i.e., the membrane could be easily manipulated. Handling membranes with thicknesses of 14, 24, and 35 μm was much more difficult than the 7 μm membrane. Stronger membranes demonstrated self-elasticity such that the membrane shrank and did not hold the desired shape after cutting the membrane to the desired shape and size. We considered these thicknesses inappropriate and therefore continued our research using a membrane thickness of **7** μm. The nanofiber membrane cannot be placed directly on the skin for two reasons. The membrane does not have sufficient mechanical strength or sufficient adhesion. If the membrane was left on the skin without further fixation, it would be very easily dislodged. Therefore, the membrane must be combined with a suitable carrier having the following characteristics:

a. sufficient adherence to the skin to prevent easy removal,

b. sufficient mechanical strength to protect the membrane from damage,

c. suitable transparency, i.e., to allow light to access to the membrane.

Based on an analysis of the different types of dressings, we decided to use Tegaderm polyurethane film. It is a transparent, breathable, and semipermeable dressing. After application of the 7 μm thick Nano fiber membrane (made of polyurethane enriched with 1% (w/w) TPP) to the Tegaderm film, we measured the production of singlet oxygen immediately after preparation and after skin exposure.

These measurements showed that:

a. considerable amounts of singlet oxygen (above 100 pulses) were being produced,

b. production of singlet oxygen was not impaired by contact with the polyurethane film,

c. Singlet oxygen production was not impaired by skin contact for 1, 6, 12, and 24 hours.

Testing also showed that singlet oxygen production does not interfere with alcohol disinfection of the skin.

Measurements of Bactericidal Effects

The basis for the practical applicability of the developed dressing system is its ability to act bactericidally, i.e., to kill live bacteria in the immediate vicinity of the Nano fiber membrane. To verify this capability, we applied the dressing system for 2 and 4 hours and indirectly using the imprint method, we evaluated semi-quantitatively the reduction in bacterial flora compared to the normal state. Test results showed that the dressing system had significant bactericidal effects. The ability of singlet oxygen to penetrate outside the Nano fiber membrane and oxidize external substrates was an essential feature and proved to be effective.

Selection and testing of the optimal light source

Prior to in vivo testing, it was necessary to determine the optimal light source for inducing singlet oxygen production. We defined the properties of the required source and produced two variants. We verified (using a certified laboratory) that the light sources had the required properties and established the safe conditions for their use. Two manufactured lamps [15] the LED REFREKTOR 10W SMD LED 410–420 nm and [8] the REFREKTOR 10W Cree LED 420 nm LED have been awarded calibration certificates and passed health-related safety tests for use as medical devices. Measured values were processed according to standards. Both lamps are in group 2; i.e., a medium hazard, avoid looking directly at the light source, use with glasses rated for blocking UV and blue lasers (i.e., in the range of 200–480 nm) for long-term observation of objects under this light. We decided to use the SMD lamp, with a wavelength around 420 nm, because at this wavelength the porphyrin used has the strongest absorption in the visible spectrum.

In vitro tests - verification of the bactericidal efficiency of the dressing system when illuminated using the selected (SMD) light source

Prior to verifying the testing of Nano fiber TPP dressing in animals, it was necessary to verify its effectiveness at inhibiting in vitro bacterial growth of normal micro flora on human skin. Through testing, we demonstrated that a 10W SMD LED 410–420 nm LED held 10 cm from the skin for 10 minutes had a positive bactericidal effect on the growth of Staphylococcus aureus, Pseudomonas aeruginosa, and Staphylococcus epidermidis colonies. The bactericidal effect of this lamp was demonstrated after 1 minute in all strains except for Escherichia coli, where the loss occurred at 3 minutes. Similarly, bactericidal activity was demonstrated for 10 minutes after illumination of the membrane, and the area of the exposed membrane was colony-free for all three strains, except for Escherichia coli (Table 1).

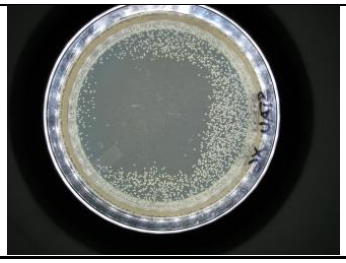
Bacterial strain	Lamp X	
Staphylococcus aureus Control test: Without lighting with nanofiber: 	5’	
	1’	
	10’	

Table 1: *In vitro* tests.

In vivo tests - verification of the properties of the dressing system

Other features of the Nano fiber membrane tested included a sensitization test, irritability test, photo toxicity, and penetration.

a. Sensitization test

Skin sensitization is an immunologically mediated skin reaction to the substance. In humans, the reaction is characterized by itching, redness, swelling, pustules, blisters, bubbles, or a combination of symptoms. For other species, reactions may vary, and redness or swelling can be detected, for example. To test sensitization of the Nano fiber membrane, we used the ears laboratory mice. The Nano fiber membrane extract was prepared according to standards in an extraction ratio of 6 cm^2/1 ml with the extraction agent being a polar-physiological solution and non-polar cottonseed oil. Extraction was performed at 37 ° C for 72 hours, at 100 rpm. For testing, 20 healthy, young (9 weeks old) and adult laboratory female mice were used. The basic principle is that sensitizers induce a primary proliferation of lymphocytes in the lymph nodes of the draining sites of the test material, i.e., the dorsal part of the ears. The number of proliferating cells in the lymph nodes is determined by measuring the content of ATP (nucleotide - adenosine triphosphate) in cells, using the bioluminescence method. The behavior of the animals during the experiment was normal. There was no significant weight loss, and no signs of systemic toxicity were observed. Redness, skin irritation, swelling, etc. were also absent from the application site.

Overall assessment of the trial (no clinical picture, signs of irritation, signs of systemic toxicity, ear erythema, skin irritation at the application site, scratching of the ears, etc. were observed) was that the substance does not produce systemic toxicity, was non-irritating, and had no sensitizing potential.

b. Penetration test on skin

The principle of the test is based on the assumption that the substance being tested can penetrate the stratum corneum and epidermis and reach a recipient fluid. The method consists of applying sample of porphyrin-containing nanofiber membrane to a three-dimensional human skin model EpiDerm ™, which is an organotypic *in vitro* human epidermis model consisting of a reconstructed epidermis with functional corneal layers (stratum corneum). The measurement results showed that porphyrin was not detected in the tested media

samples after the *in vitro* skin penetration test, and therefore did not penetrate the skin.

c. Test of phototoxic effects on *in vitro* skin

Phototoxicity is defined as an acute toxic response induced in the skin after the test substance is exposed to UV or visible radiation. The test was performed on a reconstructed human skin model. If tissue viability after application of the test substance and irradiation is 30% or more over the non-irradiated tissue, the substance is considered to be phototoxic to the skin.

The result of the *in vitro* phototoxicity assay using reconstructed human skin models showed that the nanofiber material with porphyrin had no phototoxic potential when applied to human skin.

d. *In vitro* phototoxicity assay on cells (mice fibroblasts)

The fluorimetric method of determining cell life is based on the incorporation of a vital dye into live cells and detection of fluorescence after excitation (53 nm) and emission filter (590 nm) when cold light is passed through the cells. The test results showed that the extract from the test item (porphyrin-containing nanofiber material) had no phototoxic potential, neither is it cytotoxic nor phototoxic even when tested with its highest test concentration (100% extract without further dilution).

e. *In vitro* skin irritation test on the EpiDerm human skin model

The principle of the test is based on the assumption that irritants can penetrate the stratum corneum through diffusion and are cytotoxic to the cells in the underlying layers. The test substance is considered as irritating to the skin if the viability of the tissue after exposure and subsequent post-incubation is less than or equal to 50%. Test samples after exposure to porphyrin Nano fibers showed that they were not irritating to the skin.

Conclusion

The innovative nature of our solution lies in the exploitation of the unique properties of Nano fibers in combination with anti-microbial effects of singlet oxygen. The new dressing compares favorably to the currently available dressing materials that depend on the antimicrobial effects provided by antibiotics or disinfectants (e.g., chlorhexidine). In vitro tests using a 7 μm thick Nano fiber membrane treated with TPP photosensitizer and producing singlet oxygen demonstrated that the new dressing system to be both safe and effective. Singlet oxygen production was not affected by contact with alcohol-based disinfectant solutions and was shown to have bactericidal effects after 3–10 min of light relative to commonly occurring bacteria found on human skin. The most suitable light source for inducing singlet oxygen production was the SMD LED 10W 410–420 nm held at a distance of 10 cm for a period of 10 minutes, which is user-friendly procedure suitable for any medical practice. In vivo tests (on laboratory mice and human skin model) have shown that the Nano fiber membranes supplemented with TPP is non-irritating to the skin, does not sensitize, is not phototoxic, and does not penetrate the skin. Thus, it has the prerequisites for use in clinical practice as a medical device. The next step will be clinical testing of the Nano fiber dressing to cover invasive access sites. We have reason to expect that the new dressing system will reduce the number of complications, reduce the number of nosocomial infections, and increase the quality of care for patients. This prototype of dressing material was submitted as a utility model to the Industrial Property Office.

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