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Evaluation of polymer and self-assembled monolayer-coated silicone surfaces to reduce neural cell growth

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Abstract

The development of silicone catheters has improved the treatment of hydrocephalus. Unfortunately, the functionality of the catheters used for the treatment of hydrocephalus is compromised by cell obstruction. In this study silicone surfaces coated with biopolymers (heparin and hyaluronan) and self-assembled monolayers (SAM) (octadecyltrichlorosilane—OTS and fluoroalkylsilane—FAS) were employed to investigate the effect of these coatings on astrocyte and choroid plexus cell growth in vitro. Compared to unmodified silicone, FAS surfaces significantly reduced ($p<0.05$) astrocyte proliferation, heparin ($p<0.001$) and hyaluronan ($p<0.001$) surfaces significantly increased astrocyte growth, while no significant difference was observed on OTS surfaces. A similar trend was observed for choroid plexus cell growth on heparin ($p<0.05$) and hyaluronan ($p<0.05$) coatings, however, no significant reduction in cell growth was observed on FAS- or OTS-coated surfaces compared to silicone. Low cell growth may be attributed to hydrophobicity of the surfaces (FAS $112.2\pm2.6^\circ$, OTS $102.2\pm1.3^\circ$). Contact angle measurements confirmed the stability of the hydrophobic and hydrophilic properties of all the coatings on the silicone surfaces for 30 days. Surface roughness did not play an important role on cell growth. Silicone shunts coated with SAMs may be suitable for future clinical applications to improve the treatment of hydrocephalus.

Keywords: Cell growth; Self-assembled monolayer coatings; Polymers; Silicone catheters; Hydrocephalus shunts

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1. Introduction

Silicone shunts have been used for 50 years for the treatment of hydrocephalus. Continuous research and improvements have been made to the shunt system over this time. Nevertheless, the problems of shunt complication and failure still remain a serious issue, often requiring several surgical procedures to re-establish a functioning shunt. According to a retrospective study on cerebrospinal fluid shunting in the United States that reviewed the Nationwide Inpatient Sample (NIS) database for the year 2000, 40.7% of all procedures considered in the study were shunt malfunctions. The total cost related to the shunt procedures (primary and secondary) was $1.1 billion [1]. The most common shunt complications are obstruction and infection [2–4] leading to mortality and morbidity in the treatment of hydrocephalus [4–7]. Retrospective analyses of the charts of 94 children between the years 1993 and 2003 concluded that the most common complication was shunt blockage (30%) and the most frequent area of blockage was within the intraventricular component (90%) [8]. Various tissues and materials can lead to proximal shunt obstruction. Epithelial cells of the choroid plexus [2,9–11] and astrocytes are especially capable of

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proliferation and have been shown to fill the holes and lumen of the catheter [11]. The only remedy, to overcome the after effects of shunt blockage is removal of the old blocked shunt and replacement with a new shunt. A potential solution to this problem may be to coat the silicone surface of the shunts with biocompatible polymers, possibly having additional antimicrobial properties that considerably reduce the growth of cells and bacteria. There are no consistent data available from adequately sized, randomized and controlled trials for coated shunts. Clearly more research is needed on the cost-effective coatings of shunts.

Various studies with polymer coatings have been attempted to reduce cell growth on the implant surface. Heparin, a well-known anti-coagulant, is a natural polysaccharide and frequently used as a surface coating agent to improve blood-material compatibility. Studies by Zareie et al. [12] using heparin-coated silicone peritoneal catheters and Lev et al. [13] using heparin-coated stents demonstrated that coated surfaces had a lower failure rate compared to uncoated surfaces. When implanted for 5 days in rats, the catheters coated with heparin were reported to be less adhesive compared to conventional catheters. The drop out rate was 57% (8/14 animals) for regular silicone catheters because of omental wrapping around the tip of the catheter. This was compared to heparin-coated catheters, which had a dropout rate of only 20% (3/15 animals) [12]. Hyaluronic acid (HA), which has a heparin-like property, is used in hydrophilic coatings for a variety of medical devices, including catheters to improve biocompatibility and reduce cell and bacterial adhesion [14]. Pavesio et al. [15] concluded that the covalent binding of hyaluronan to the surface of biomedical materials could yield an anti-adhesive surface that resists adhesion of proteins, bacteria and cells. Another biocompatible polymer is *N*-octadecyltrichlorosilane [$CH_3(CH_2)_{17}SiCl_3$] (OTS), which is useful for its hydrophobic properties. Prior research with LRM55 cells cultured on OTS and *N*-(3-(trimethoxysilyl)-propyl)-diethylenetriamine (DETA, hydrophilic) coatings on silicon substrate for 6 h demonstrated that less cells adhered to OTS compared to DETA [16]. Perfluorodecyltrichlorosilane [$CF_3(CF_2)_5(CH_2)_2SiCl_3$] (FAS) is another polymer with hydrophobic properties and has been used by previous researchers to study cell adhesion in relation to hydrophobicity. Stenger et al. [17] have been able to direct the polarity of embryonic hippocampal neurons by manipulating the patterns of aminosilane self-assembled monolayers (SAM) on a background of FAS. Neurons avoided the FAS-coated portions of the pattern, suggesting that FAS reduces cell growth. Thus, previous studies on polymer coatings have demonstrated that coating the implant surface with polymers can reduce cell growth, which may minimize shunt obstruction.

Although previous studies have demonstrated that biopolymer coatings such as heparin, hyaluronan, OTS, and FAS improve the blood compatibility of medical devices, there are no recent systematic studies of silicone coatings that evaluate brain cell proliferation. Currently there are no polymer-coated shunts for hydrocephalus in the market, which in theory would have reduced cell growth thereby reducing blockage of the shunt. Therefore for this study, we used heparin, hyaluronan, OTS and FAS as coating materials for silicone. We hypothesize that coating the silicone catheter with SAMs or biopolymers would reduce cell growth on the shunt surface thereby reducing the chances of shunt obstruction and failure.

2. Material and methods

Silastic silicone sheets (thickness: 0.015 in) were obtained from Dow chemicals (Midland, MI) and cut into disks (diameter: 21 mm per sample). OTS (97.5%) was purchased from United Chemical Technologies (Bristol, PA). Heparin and HA were purchased from Sigma (St. Louis, MO). FAS (97.5%), 1-3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (98% water-soluble carbodiimide, WSC), and 4- azidoaniline hydrochloride (97%) were obtained from Aldrich Chemicals (St. Louis, MO). All chemicals were used without further purification.

2.1. Coating

2.1.1. Surface modification of silicone with OTS

Silastic silicone disks were cleaned by immersion in pure ethyl alcohol in a Branson 2200 ultrasonic cleaner for 5 min, and dried with nitrogen. The silicone disks were then treated by a plasma cleaner (Harrick Scientific, PDC-32G) for 5 min. Subsequently, the plasma-treated disks were placed together with OTS in a glass container and placed into a sealed chamber at 10^{-3} Torr at room temperature for 4 h. The silicone disks were kept in the sealed chamber with OTS for an additional 12 h.

2.1.2. Photo-immobilization of heparin and hyaluronan on OTS modified silicone

Heparin, WSC, and 4-azidoaniline hydrochloride at a weight ratio of 2.35:1.29:1 were dissolved in deionized water to make a 0.5% solution. The pH of the solution was adjusted to 4.70–4.75 using 2.3 N NaOH and 0.1 N HCL solutions, and then stirred at 4 °C for 24 h. A 0.2% aryl azido-modified hyaluronan solution was prepared by the same method except that the weight ratio was 42:28:17.06. All the reactions were carried out in a dark room. The OTS on silicone samples was illuminated with a mercury vapor UV lamp (175 W, Regent Lighting, Burlington, NC) for 10 min at a distance of 10 cm in the presence of the aryl azido-modified heparin and hyaluronan solution. The samples were then rinsed by immersion and washing with deionized water for 48 h.

2.1.3. Surface modification of silicone with FAS

Silicone disks were prepared by plasma cleaning as described above. FAS was then deposited on the silicone surface by chemical vapor deposition for 5 min under a vacuum of 10^{-3} Torr. The samples were then maintained in the sealed chamber for an additional 4 h.

2.2. Surface characterization

2.2.1. Contact angle measurement

Contact angles of silicone and modified silicone samples were determined by a NRL contact angle goniometer (Model 100, Ramehart,) at ambient pressure. A water droplet of approximately 20 μl was placed on the substrate and the contact angles were measured on both sides of the droplet. Three droplets were placed at various spots on the substrate surfaces and the average readings were recorded.