

Biofilm Prevention By Surface Acoustic Waves: A New Approach To Urinary Tract Infections – A Randomized, Double Blinded Clinical Study

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Catheter associated urinary tract infection (CAUTI) is a major cause of morbidity and mortality in hospitalized patients. The longer the catheter remains in place, the greater the tendency of certain organisms to develop biofilms, resulting in CAUTI's and antibiotic resistance. Various solutions were developed and evaluated for reduction of CAUTI including coatings (mainly Silver-oxide), closed systems, antimicrobial ointments, lubricants and others. However, there is lack of clinical evidence for the efficacy of these methods. We report here on a new technology aimed at reducing the formation of biofilm. This innovative approach utilizes low frequency/low intensity ultrasound. This technology is embodied in a new device (UroShield™, NanoVibronix Inc., USA) that is clipped onto the urinary catheter and is designed to prevent biofilm by creating low-energy surface acoustic waves (SAW) on the inner and outer surfaces of the indwelling urinary catheter. A randomized, double blinded clinical study was carried out in 22 subjects (11 subjects in each group) requiring a urinary catheter. Following retrieval, the catheters were evaluated for the presence of biofilm by scanning electron microscopy. No biofilm was found on the surface of the catheters that were connected to the UroShield device while 7 of the 11 control catheters were covered with biofilm. These results show that this new technology can markedly reduce biofilm formation on urinary catheters and may become a standard tool to diminish CAUTI.

Introduction

Microorganisms in nature may be found in two principal forms of life: (A) free, single cells in a liquid (planktonic) and (B) as a sub-population of clusters (biofilms) adherent to a living or inert surface and encapsulated within an Extracellular Polymeric Substance (EPS) (1).

The placement of a Foley catheter is a known cause for biofilm formation. Within a few hours of Foley placement, bacteria begins to attach to the catheter surface thus beginning the cascade of biofilm formation. Biofilm is felt to be the cause of many of the complications associated with Foley catheterization such as infection and catheter clogging. According to the National Nosocomial Infections Surveillance (NNIS), hospital-acquired infections affect approximately 2 million persons per year across the United States. In addition, in European Union countries there are 3 million nosocomial infections yearly accounting for 50,000 deaths out of the 99,000 total deaths yearly from infection. According to the 2007 Centers for Disease Control and Prevention Report, these infections are distributed as follows: 32% - urinary tract infections; 22% - surgical site infections; 15% - lung infections (pneumonia); 22% - blood stream infections (2). Moreover, infections caused as a result of biofilm formation are characterized by particularly strong antibiotic and immune resistance patterns. The urinary catheter is a primary source for such infections due to the colonization of bacteria on the catheter surface and the creation of biofilm (3,4). The longer the catheter remains in place, the greater the tendency of these organisms to develop biofilms, thus the greater risk of urinary tract

infections. The incidence of bacteriuria in patients with urinary catheters is approx. 5% per day, with virtually all patients who undergo long-term catheterization (>28 days) becoming infected. Microbial biofilms also present serious challenges to the immune system, because expression of bacterial antigens within the encasing polysaccharide matrix is suppressed and the colonies are highly resistant to phagocytosis by polymorphonuclear cells (5). Altogether these properties render biofilms exceedingly difficult to eradicate and explain the severity, persistence, and high levels of morbidity associated with the infections that they produce.

In this study, we have tested the potential of a new device, the UroShield low frequency/low intensity ultrasound system, in preventing biofilm formation on indwelling catheters in subjects requiring urinary catheterization. The UroShield is a battery operated, portable device that creates low intensity/low frequency Surface Acoustic Waves (SAW) on the catheter. These acoustic waves propagate along the inner and outer surfaces of the indwelling urinary catheter creating an acoustic envelope in order to prevent bacterial adhesion to the surfaces of the catheter, hence reduce biofilm formation. To the best of our knowledge, this is the first attempt to use physical means in a clinical setting for prevention of biofilm formation on indwelling urinary catheters.

Materials and Methods

The UroShield Device

The UroShield is designed as a low cost, disposable device that is added onto a conventional urinary catheter.

The UroShield system is comprised of two main components: (A) The disposable UroShield Actuator - a disposable, small, lightweight, clip-on actuator that is attached to the external part of the urinary catheter after the catheter has been inserted into the patient. The actuator is powered by the UroShield Driver allowing it to create the ultrasonic surface acoustic waves on the catheter surfaces. (B) The UroShield Driver is an external driver unit that is attached to the UroShield Actuator. The driver unit includes programmable electronics that control the actuator unit and is battery powered. The driver is small, lightweight and may be placed on the patient bed or worn on a belt if the patient is ambulatory.

The aim of the UroShield is the prevention of biofilm formation by blocking the initial step in biofilm formation - docking of bacteria on the surface of the catheter. The UroShield accomplishes this by creating low-energy surface acoustic waves on the inner and outer surfaces of the catheter. This coating physically blocks the planktonic bacteria from attaching to the catheter surface thus aborting the biofilm formation cascade. The UroShield may also disrupt the bacterial chemotactic signaling mechanism, which promotes organization of bacterial communities needed to build biofilm.

Study design

This was a randomized, double blinded, sham controlled comparative trial. Independent evaluation of the catheters for biofilm was performed. A sample size of N=22 (11 in each group) was determined to be adequate to demonstrate large differences between the groups, at a significance level of $p < 0.10$. This p-value was used to protect against false negatives, and to increase sensitivity to deviations from equality between the control and active group. Recruitment was continued until a quota of 22 subjects was achieved. A subject who either had a positive urinary culture at baseline or had his catheter removed after less than five days was to be replaced until twenty-two valid subjects had been recruited.

During the study, 11 subjects received the UroShield device (NanoVibronix Inc., USA) while 11 subjects received a sham device. All subjects in the trial were post-urological surgery. The sham UroShield system looked and reacted identically to the active system—including alarms and LEDs, aside from the fact that the actuator was not electrified.

Study procedures

The overall plan consisted of the following steps:

1. Subjects were assessed for their eligibility to participate in the study according to the inclusion/exclusion criteria and signed a written informed consent according to Declaration of Helsinki and local regulations.
2. A randomization procedure was performed in order to determine the subject's study group.
3. The urinary catheter was inserted following the surgical procedure and the UroShield device was connected to the external segment of the catheter and activated throughout the study period (until catheter withdrawal).

4. Analgesic intake was recorded for all subjects. A comparative analysis of the groups was performed in regards to analgesic usage.

SEM analysis

At termination of the study, the urinary catheters were fixed in 4% buffered formaldehyde. Three sections of 1 cm each were cut from the catheters as following: (a) 1cm proximal to the balloon (b) 2cm proximal to the first section and (c) 1cm from the actuator (2cm from the body). The catheters sections were cut into halves and the outer and inner lumens were observed. On each catheter sample, three different random points in an oblique line were examined at three magnifications: x15, x500 and x3500.

Study objectives

This study was aimed to assess the safety, tolerability and prevention of biofilm formation in subjects that required urinary catheter following urological surgery.

Study endpoints

The endpoints of the study were:

1. Lack of adverse events and/or serious adverse events.
2. Lack of device-associated complaints or discomfort.
3. Prevention of biofilm formation.
4. Reduction in analgesic intake.

Statistical analysis

All demographics and medical history variables were tabulated for the individual subjects. Due to a small sample an effort was made to present the entire data for easy visual viewing. No formal statistical analysis was used due to the small size. Safety data (see below) were tabulated for each subject and for each group. The efficacy exploration included data tables per subject over time in a graphical manner exhibiting the follow-up period, and the relevant data.

Results

Demographic analysis

22 subjects were enrolled into the study during a period of 4 months. All subjects were males. The mean age was 68.0 ± 9.1 (range 49.1-78.9) and 63.1 ± 9.8 (range 40.3-76.9) for the active and the control groups, respectively. No differences were found in the vital signs and the blood chemistry/hematology between the active and the control groups, prior to and following catheter insertion and withdrawal. The clinical diagnosis of the subjects is described in table 1.

Table 1 – Primary reason for hospitalization

Reason	Active Group		Control Group	
	N	%	N	%
Prostate Cancer	7	64%	9	82%
Kidney Cancer	3	27%	1	9%
Kidney Cyst.	1	9%	0	0%
Tumor of Penis	0	0%	1	9%
TOTAL	11	100	11	100

Catheter analysis

Average catheter days were 8.8±2.7 and 9.2±2.2 days for the active and the control groups, respectively (range was 5-13 days). The catheter diameter varied from 14" (French) to 20". In addition, there were two major types of catheters used in this study: double-lumen and triple-lumen catheters. Triple lumen catheters have a channel for irrigation, which might reduce the likelihood of bacteriuria and biofilm development. Table 2 represents catheter size and type distribution.

Table 2 – Catheters size & type distribution

Catheter diameter	Active Group		Control Group	
	N	%	N	%
14"	7	64%	9	82%
16"	3	27%	1	9%
18"	1	9%	0	0%
20"	0	0%	1	9%
Catheter type				
Double lumen	4	36%	3	27%
Triple lumen	7	64%	8	73%

Adverse events

One subject within the active group had a Stroke. It was defined as unlikely related to the study device. It should be noted that this subject had a cardiovascular medical history including a previous stroke in the previous year. UroShield therapy was continued as he recovered from this event.

One subject in the control group suffered from occlusion of the catheter on day 3. This was an event of moderate severity but was considered unlikely to be related to the study device. There were two additional adverse events in the control group and three adverse events in the active group. All were classified unlikely to be related to the study device.

Biofilm formation

SEM analysis by a certified pathologist showed biofilm on seven catheters from the control group while no biofilm was observed in any of the active catheters, neither in the outer or inner lumen of the catheters (tables 3A & 3B).

Pain medication management

Catheter related urethral pain and bladder spasm were treated with specific medications that were given on per need basis following subject complaints. The treatment group had statistically significant less consumption of these types of analgesics, indicating a reduction in pain levels during the study period. A total of 2 voltaren and 2 spasmex were prescribed for the active group in comparison to a total of 6 voltaren and 12 spasmex prescriptions for the control group, throughout the study.

Table 4 shows an analysis of daily pain management medications in the control and the active groups. In the control group, 16.8% of catheter days subjects were administered pain relief medications for catheter related pain and discomfort; this is in comparison to only 4.1% of subjects-days in the active group. This finding is statistically significance with a p=0.003.

Table 3 - SEM analysis of the catheters within the active group (A) and the control group (B)

Active group (A)	Subject	Biofilm presence	SEM
N = 11	3	-	
	4	-	
	5	-	
	6	-	
	10	-	
	12	-	
	13	-	
	15	-	
	17	-	
	20	-	
	22	-	
Total Biofilm Presence		N = 0	

Control group (B)	Subject	Biofilm presence	SEM
N = 11	1	+	
	2	+	
	7	-	
	8	-	
	9	+	
	11	-	
	14	-	
	16	+	
	18	+	
	19	+	
21	+		
Total Biofilm Presence		N = 7	

Table 4 – Days of pain management medication

		Active (n=11)	Control (n=11)
Days	Rx-	93	84
	Rx+	4 (4.1%)	17 (16.8%)
Total days		97	101

Note - Rx+ indicates medication obtained for bladder pain management includes: Voltaren and Spasmex. Chi square test was highly significant with P=0.03

Discussion & Conclusions

Biofilm can form on a variety of biotic and non-biotic surfaces in liquid media e.g. living tissue, medical device, industrial tubing, cooling towers or watercraft (1).

There are several hypotheses attempting to elucidate the advantages of biofilm formation for bacterial survival over the singular cell life. One of those hypotheses is based on the fact that physical conditions on the substrate are more suitable for colonization and growth. In addition, the EPS improves homeostasis and provides certain protection from the adverse environmental factors such as UV radiation, toxic metals and phagocytosis (5).

We believe mechanical vibration energy interferes with early events in the biofilm development process, mainly the adhesion of planktonic microorganisms to surfaces. In an era where there is strong interest in curtailing use of antibiotics, using physical measures constitutes a good strategy for the serious clinical problem of biofilm formation. The UroShield device proved to be safe and well tolerated with no differences in adverse event rate between the groups. Moreover, it appears that the UroShield reduces pain and spasm levels, thus less medication is required to treat these catheter related symptoms.

The main finding of this study is that the surface acoustic waves can markedly reduce – or even eliminate – the level of biofilm formation within indwelling catheters while a high rate of biofilm (7 out of 11) can be found in the control group. To the best of our knowledge, this is the first time that such a phenomenon is described in the literature. Thus, the results indicate that low frequency/low intensity ultrasound has enormous potential to prevent those early processes that eventually lead to the formation of biofilm. This approach opens new options for non pharmacological prevention of urinary tract infections (7).

Biofilm formation on various implanted devices has recently become a focus of intense research. As our population ages, there will be an increase in the number of people experiencing hospitalization and requiring biomedical implants. Therefore research into non-invasive modalities of biofilm prevention may achieve both economic and clinical improvements for health care providers.

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