Clinical Trial Report

The Use of the UroShield Device in Patients with Indwelling Urinary Catheters

Protocol US-71-003

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Version: 2

This report complies with Guidelines for Industry: Structure and Content of Clinical Trial Report. ICH E3 E3 www.ICH.org and ISO 14155-1,2:2003

STUDY SYNOPSIS

Sponsor company	NanoVibronix
Product	UroShield
Title of study	The Use of the UroShield Device in Patients with Indwelling Urinary Catheters
Study number	Protocol US-71-003
Investigator	Dr. Ofer Shenfeld
Study center	Shaare Zedek Medical Center, Jerusalem, ISRAEL
Study period	First subject enrollment –07/05/2007 Last subject follow-up – 01/03/2009
Objectives	Safety Objectives:

To assess the safety parameters of the UroShield system

Efficacy objectives:

1. **Primary objectives**

To observe the effect of UroShield in the reduction of patient's complaints relating to indwelling urinary catheters

- Pain
- Discomfort
- To observe the effect of UroShield in the reduction/prevention of Biofilm
- To observe the effect of UroShield on the occurrence of bacteriuria and/or UTI's on patients with indwelling urinary catheters[1]

[1] Note: the Helsinki committee approved this clinical trial for up to 210 patients. During the trial the company made a decision to begin marketing the UroShield device as an accessory for the reduction of urinary catheter related pain , discomfort and spasm, as prior studies supported. Therefore it was elected to close the trial at 40 patients and examine the evidence. In the future the company may elect to expand the claims to include prevention of UTI and bacterial biofilm, because initial indications for this are promising. However it will take significantly more patients. The last 2 objectives were not considered in this trial, because of the insufficient sample size. It is known in the art that nosocomial bacteriuria develops only in up to 25% of patients requiring urinary catheter for > 7 days[1]

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2. Secondary Objectives

- To observe the effect of UroShield in reduction of Foley Catheter related pain medication in patients with Indwelling Urinary Catheters
- To observe the effect of UroShield in reduction of antibiotic medication in patients with an indwelling urinary catheter
- To observe the effect of UroShield on the clogging of urinary catheters when used chronically and the need to replace the catheter
- To observe the effect of UroShield on the decrease of tissue damage of patients with indwelling urinary catheters by measuring cell count before and after removal of catheter

Methodology This is an open label, comparative, randomized trial

Number of subjects 40 subjects[2]

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Treatment duration Treatment duration was up to 13 days per subject

Endpoints

Safety Endpoint:

- Lack of device related adverse event and Serious adverse event

Efficacy Endpoints:

- Patient complaints related to catheter regarding pain according to VAS scale and discomfort according to 0-10 scale
- Presence of Clinically Significant UTI
- Presence of Bacteriuria
- Presence of Biofilm[3]

[2] Note: the Helsinki committee approved this clinical trial for up to 210 patients. During the trial the company made a decision to begin marketing the UroShield device as an accessory for the reduction of urinary catheter related pain, discomfort and spasm, as prior studies supported. Therefore it was elected to close the trial at 40 patients and examine the evidence. In the future the company may elect to expand the claims including prevention of UTI and bacteria biofilm, because initial indications for this are promising.

Secondary Efficacy Endpoints:

- Use of pain medication
- Use of antibiotics
- Tissue damage
- Number of catheters changed
- Patient's complaint related to catheter (burning sensation, itching, spasm - according to 0-10 scale)

Statistical analysis

Sample characteristics were tabulated, in a manner providing eye balling review of the individual patients by groups.

Statistical analysis between groups was perfrormed using student's T-test (paired samples, one tail, equal variance) with P-value of 0.05 in order to determine the difference between pain , discomfort and spasm levels in active patients and controls.

Conclusions

This randomized controlled trial showed the UroShield device to be effective in reducing post operative catheter related pain discomfort and bladder spasms. There was also a notable trend towards reduction of bacteriuria. The UroShield device as an accessory for the catheter was shown to be effective in reducing pain, discomfort and spasm associated with an indwelling urinary catheter: the severity of pain was reduced by 31%, discomfort by 30% and spasm by 32% in the Active Group with UroShield device in comparison to the Control Group without the UroShield device. This difference was found to be statistically significant (two-tailed

[3] Note: as mentioned above, the Helsinki committee approved this clinical trial for up to 210 patients. During the trial the company made a decision to begin marketing the UroShield device as an accessory for the reduction of urinary catheter related pain, discomfort and spasm, as prior studies supported. Therefore it was elected to close the trial at 40 patients and examine the evidence. In the future the company may elect to expand the claims including prevention of UTI and bacterial biofilm, because initial indications for this are promising. However it will take significantly more patients than 210. The last 2 objectives were not considered in this trial, because of the insufficient sample size. It is known in the art that nosocomial bacteriuria develops only in up to 25% of patients requiring urinary catheter for > 7 days[1].

Student t test was used, $p < 0.05$) .

85% patients from control group and 57% patients from active group received pain and spasm medications. Comparison of pain and spasm relief medications strength was in favor of the Active Group: 3.7 in Control Group versus 3.4 in Active Group

There was a notable trend towards reduction of bacteriuria. Urine cultures on 3rd day revealed bacteriuria in only 5.3% of the UroShield patients compared to 10% of the controls. The number of subjects from day 6 and onward was insufficient for estimating the rate of bacteria.

Table of content

1 Introduction

1.1 Background

The UroShield™ device (an accessory for the indwelling urinary catheter) delivers low frequency ultrasound and acoustic lubrication to the surfaces of an indwelling Foley Catheter and to the tissue surrounding the catheter. The indwelling urinary catheter receives the benefits of low frequency, low intensity ultrasound including: prevention of biofilm, increased antibiotic efficacy in the catheter lumen and decreased pain, spasm and discomfort associated with the use of the catheter.

The UroShield device decreases adherence of bacteria to catheter surfaces thereby reducing biofilm. Biofilm is the complex matrix required for bacteria to grow and cause infection. Independent *in-vitro* studies have demonstrated that UroShield increases antibiotic efficacy greater than 95% within the inner lumen of a Foley catheter. An anti-clogging effect is achieved by ultrasound waves creating an acoustic layer on the inner lumen of the urinary catheter thereby preventing adherence of biological material and is essential in preventing local infection and sepsis secondary to catheter obstruction.

Acoustic lubrication is a well known physical consequence of application of acoustic energy to surfaces. In the case of UroShield, the acoustic envelope created on the surfaces of the urinary catheter decreases friction between the urethra and the urinary catheter and therefore, as shown in animal studies, reduces tissue trauma caused by the catheter. In addition to decreasing pain, spasm and discomfort associated with catheters, the tissue in contact with the catheter remains healthier and less traumatized as a result of the application of acoustic lubrication on the catheter surfaces.

1.2 The UroShield Device

The UroShield device (an accessory to a Urinary catheter) transmits low frequency low intensity ultrasound, in the form of Surface Acoustic Waves, to all catheter surfaces. It can be used with any type of indwelling urinary catheter regardless of the material or coating.

The NanoVibronix UroShield device, is comprised of 2 main components:

- **Disposable UroShield Actuator** - a disposable small, lightweight clip-on accessory that is attached to the external portion of the urinary catheter after the catheter has been inserted into the patient. The actuator receives energy and a electrical signal from the UroShield driver and creates the acoustic lubrication effect on the catheter surfaces.
- **UroShield Driver** - an external driver unit that is electrically connected to the UroShield actuator. The driver unit contains batteries to power the system and electronics that control the UroShield actuator. The driver is small, lightweight and may be placed on the patient bed or worn on a belt if the patient is ambulatory.

2 Study Rationale

According to the Israeli Ministry of Health requirement, this study was designed to evaluate the efficacy of the UroShield system is patients that require urinary catheterization. This was designed to compare standard treatment (urinary catheter alone) with the use of a catheter and UroShield treatment in occurrence of catheter associated urinary tract infection, pain, discomfort, spasm and biofilm prevention.

3 Study Design

3.1 Overall design

This was an open label, comparative, randomized trial to assess the effectiveness of the UroShield device, attached to a 14 Fr - 22 Fr siliconized latex urinary catheter, in comparison to a 14 Fr - 22 Fr siliconized latex urinary catheter alone, in the therapy of urinary catheter related pain , discomfort and spasm, as well as in the prevention of bacteriuria or UTI and reduction of biofilm.

The overall plan for all patients consisted of the following elements:

1. Patients were assessed for eligibility to participate in the study and signed a written informed consent, according to Declaration of Helsinki and local regulations.
2. Urine cultures were collected at baseline and every 3 days. Additionally, urine cultures were taken just before insertion and just after removal of the catheter.
3. Urine for total cell counts were collected at baseline and every 3 days, as well as just before and just after removal of the catheter. The urine cell count was done by a central lab using the automated IRIS system. The urine was also dipsticked and the dipstick read by the IRIS system obviating the need for another dipstick that day.
4. Patients meeting study inclusion criteria were randomized in a ratio of 2:1 (active: control) for the fixation of a urinary catheter with an active UroShield device attached to a urinary catheter or a urinary catheter alone (control)
5. During the treatment period the UroShield device was maintained by replacing the driver every 48 hours (for charging needs). The UroShield actuator remained for the treatment time.

6. Patients were required to complete a daily diary recording symptoms related to catheter such as pain, discomfort, spasm, burning and itching sensation.
7. Daily urinalysis dipstick test was performed in the hospital for WBC's when available.

3.2 Study randomization

Patients were randomized to one of the two treatment groups in a 2:1 ratio (active: control) using randomization envelopes and a randomization system in blocks of 6.

The investigator and/or the study coordinator were responsible to maintaining a log with all randomized patients and designated randomization number.

4 Study population

4.1 Inclusions/Exclusions criteria

Inclusion criteria:

- Hospitalized patients age 18 years or older
- Patients requiring or having catheterization for more than 24 hours
- Patient is able and agrees to sign the Informed Consent Form

Exclusion criteria

- Pregnant or breastfeeding women. Women of child bearing potential need to perform a pregnancy test before inclusion into the study
- Presence of any clinically relevant known urinary tract infection
- Patient with condition who is not expected to survive the study period
- Known HIV positive
- Patient has any condition, which precludes compliance with study and/or device instructions.
- Patient is currently participating in another clinical study.
- Known allergy to latex

4.2 Withdrawal criteria

Subjects were allowed to withdraw from the study for the following reasons:

- At their own request, or at the request of their legally acceptable representative.

  The investigator was allowed to withdraw a subject from the study at any time for the following reasons:

- Subjects who have problems with device (Faulty device)
- Severe side effects clearly related to the study device
- Presence or appearance of exclusion criteria
- A significant protocol violation, as determined either by the sponsor, the Ethics Committee or the investigator
- Any clinical reason at the discretion of the investigator
- At the specific reasonable request of the sponsor

5 Study Objectives

This study was aimed at assessing the effectiveness of the NanoVibronix UroShield device in comparison to Urinary catheter alone in patients requiring urinary catheterization.

5.1 Safety Objective

To assess the safety parameters of the UroShield device

5.2 Primary objectives

- To observe the effect of UroShield in reduction of patient's complaints relating to indwelling urinary catheters
  - Pain
  - Discomfort
- To observe the effect of UroShield in the reduction/prevention of Biofilm
- To observe the effect of UroShield on the occurrence of bacteriuria and/or UTI's on patients with indwelling urinary catheters

5.3 Secondary Objectives

- To observe the effect of UroShield in reduction of Foley catheter related pain medication in patients with indwelling urinary catheters
- To observe the effect of UroShield in reduction of antibiotic medication in patients with indwelling urinary catheter
- To observe the effect of UroShield on the clogging of urinary catheter when used chronically and the need to replace the catheter
- To observe the effect of UroShield on the decrease of tissue damage of patients with indwelling urinary catheters by measuring cell count before and after removal of catheter

6 Study Endpoints

6.1 Safety Endpoint

- Lack of device related adverse event and Serious adverse event

6.2 Efficacy Endpoints

Primary:

- Patient complaints related to catheter regarding pain according to VAS scale and discomfort according to 0-10 scale
- Presence of Clinically Significant UTI
- Presence of Bacteriuria
- Presence of Biofilm

Secondary:

- Use of pain medication
- Use of antibiotics
- Tissue damage
- Number of catheters changed
- Patient's complaint related to catheter (burning sensation, itching, spasm - according to 0-10 scale)

7 Data Quality Assurance

7.1 Data checking

Various data checks were undertaken using the Microsoft Office Excel database to assure that the data were entered properly and that there were no mistaken values. These involved conditional data formatting to highlight invalid values. The data checks included:

- Inclusion or exclusion criterion that was not met
- Theoretically out-of-range value (e.g., questionnaire value not between 0 and 10)
- Logically out-of-range value (e.g., heart rate not between 50 and 100 beat/min, temperature not between 35^0 and 42^0 C).

7.2 Double entry

Key variables were entered twice, by two typists subsequently. They were then compared assuring data entry quality.

8 Statistical Analysis

8.1 Study rationale

This study was designed to evaluate the effectiveness of the UroShield device in patients requiring urinary catheterization. It was designed to prove the effect of UroShield in reduction of patient's complaints such as pain, spasm and discomfort relating to indwelling urinary catheters. In addition to prove the effect of UroShield on the occurrence of bacteriuria and/or UTI's (due to the effect of UroShield in the reduction of biofilm).

8.2 Sample size

40 patients were enrolled in this study: 13 in the Control group and 27 in the Active group with UroShield device.

Sample size rationale: The UroShield device is an accessory for urinary catheter creating acoustic lubrication due to a complex of low frequency vibrations which are created on the surface of the urinary catheter. These vibrations are of a mechanical nature and have no residual effect, on the contrary to pain relief drugs which have a residual phenomenon and their action is felt for some period after the patient's usage. UroShield creates acoustic lubrication effect only when it is activated, and has no acoustic lubrication effect and resultant relief of pain, spasm and discomfort when it is turned off. These presumptions allow the measurements of each patient on each day to be considered as an independent measurement, therefore providing a sufficient sample size for statistical significance.

8.3 Statistical methods

All demographics and medical history variables were tabulated for the individual patients. An effort was made to present the entire data for easy visual viewing.

The efficacy exploration included data tables for each patient over time and a graphical manner exhibiting the median pain, spasm and discomfort data for both active and control groups.

A Student's t-test (paired samples, two tail, unequal variance) was performed to determine the difference between pain, spasm and discomfort levels for active group and control group patients.

9 Analysis Data Set

9.1 The analysis data set

The sample included measurements obtained with 40 subjects per their hospital stay with about 190 independent measurements, as it was discussed previously; 120 measurements in the active group and 70 measurements in the control group for pain level and for discomfort and spasm levels respectively. This size is adequate to demonstrate disadvantage of one group at a significance level of $p< 0.05$. This p-value protects against false negatives and increased sensitivity to deviations from equality between the control and active group.

Demographic and medical data are presented for the 40 subjects who fulfilled and completed at least 2 days of the treatment regime.

9.2 Protocol deviations

There were no protocol violations during the study.

There were minor protocol deviations during the study. The protocol allows usage of UroShield actuator for up to 22 Fr catheters. Previously to the trial, accordingly to physicians requirements minor changes were made in UroShield actuator which enabled to use UroShield actuator for catheters up to 24Fr (3 lumens).

10 Physical and Demographic Characteristics

40 subjects were enrolled to the trial and completed the study treatment regime:

Treatment (active) group, N=27; 3 women and 24 men

Control group, N=13; 3 women and 10 men

The following table summarizes the age, BMI, heart rate and blood pressure distribution (as average ± SD) between the groups within the trial.

Table 1 – Age, BMI, heart rate and blood pressure distribution by study groups

	Control Group			Active Group		
	Ave ±SD	High	Low	Ave ±SD	High	Low
Age	52±**14.45**	72	20	50±18.70	77	20
BMI	26.28±4.73	32.02	19.03	26.34±4.39	36.67	18.25
Heart rate	82.76±12.17	97	58	75.33±14.71	104	54
BP systolic	136.61±15.23	160	107	123.28±18.69	180	100
BP diastolic	79.07±11.67	107	64	74±11.31	91	55

The results demonstrate that the study groups are similar in terms of physical and medical parameters.

The groups were similar in reasons for hospitalization, catheter size and type, and number of lumens. Reasons for hospitalization in most cases were surgeries, such as: bladder tumor, urethroplasty, kidney removal, prostate, transurethral resection of prostate, urethral stricture, stress incontinence, and others. Catheter type was 2 or 3 lumen Silicone catheter, of Fr 14-24 size. Catheter size distribution over the groups is shown in the table below.

Table 2 –, catheter size distribution (as average ± SD) between the groups within the trial

	Control Group			Active Group		
	Ave ±SD	High	Low	Ave ±SD	High	Low
Catheter size	17±3.94	24	14	16±3.18	24	14

11 Safety Evaluation

11.1 Tolerability of the device

All patients reported that the device is comfortable and easy to use. No additional tolerability issues were reported.

11.2 Adverse events (AE)

18 adverse events were reported during the trial: 10 in the control group and 8 in the active group. The adverse events were followed by such conditions as: hypertention, anemia, temperature, bladder pain, catheter extruded, fever, leucocyturia and alike. The PI determined that the adverse events are unlikely to be related to the UroShield device. All patients completely recovered at the end of the trial.

11.3 Serious adverse event (SAE)

1 serious adverse event was reported during the trial with a patient from control group and was related to prolonged ventilation. The event was considered as unlikely to be related to the UroShield device and patient completely recovered.

12 Pain, Discomfort and Spasm Levels with and without UroShield

Catheter insertion was performed by the PI. Following the catheter insertion and UroShield activation, subjects were asked every day to asses their pain and discomfort level using a Zero (0) to Ten (10) scale (flicker scale/Numeric rating Scale)) whereas 0 represent no pain, discomfort or spasm and 10 represents the worst pain, discomfort or spasm.

The following tables summarize the results of the pain, discomfort and spasm levels during the study period for the two groups.

Table 3 – Mean pain, discomfort and spasm levels (as average ± SD) and reduction of these levels within the study groups (summary from the tables 3.1-3.6)

Parameter	Group	Measurement nr	Mean level	SD	Reduction %	p-value
Pain	Control	69	3.2	±2.7		0.02
	Active	122	2.2	±2.7	31%	
Discomfort	Control	69	4.0	±3.3		0.01
	Active	120	2.8	±3.0	30%	
Spasm	Control	68	3.62	±3.2		0.01
	Active	120	2.53	±2.7	32%	

Table 3.1 – Pain levels on the measurement day, number of measurements and the average pain level (± SD) within Control Group

Control subject nr	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
5	9	5	5	2	2	1							
6	4	0	0										
12			0	0									
13	0	0	0										
15	8	9	9										
16	3	7	3										
22	8	6	4	6	5	5							
23	6	3	2	3	1								
26	0	5	5										
30	0	6	4	6	6	4	0						
32	2	1	0	6	5	3							
33	0	3	5	6	4	0	0		0	0	0	0	6
40	2	2	6	2	6	2	2	4	2	0			
Measurements nr	12	12	13	8	7	6	3	1	2	2	1	1	1

Total measurements 69
Average pain level 3.2
SD ±2.7

Table 3.2 – Pain levels on the measurement day, number of measurements and the average pain level (± SD) within Active Group

Active subject nr	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
1		9	10									
2	0	0										
4	5	5	0	2								
7	2	1	2	5	0	0						
8	1	1	1									
9	7	0	0	0	0	0	0	0				
10	3	8	2	2	0	0						
11	0	0										
14	2	3	2	2	1	0						
17		5	8									
18	0	0	0	0								
19	0	3	3	4	5	2						
20	4	5	0	2	4	6						
21	0	0	0	0	0							
24	0	0	0	0	0	0						
25		5	4	4	6	3	1	3	1	1		
27	0	2	0									
28	0	0	0	0	1	0						
29	7	3	2	2	2	1	2					
31	6	6	6	5	5	5						
34	3	0	0									
35	10	7	6	5	5							
36	2											
37	0	1	1	3	0							
38	0	8	0	4								
39	1	3	1	2			1					
Measurements nr	23	25	23	18	14	11	4	2	1	1		

Total measurements 122
Average pain level 2.2
SD ±2.5

The above tables 3.1 and 3.2 for Control and Active Group show that mean pain parameter for Control Group was 3.2, in comparison to the Active Group's mean pain parameter which was 2.2. Reduction of pain parameter was by 31% in favor for the Active Group with statistical significance of presented p-value result of two side student t test p=0.01.

Table 3.3 – Discomfort levels on the measurement day, number of the measurements and the average discomfort level (± SD) within Control Group

Control subject nr	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
5	9	5	5	2	2	1							
6	4	0	0										
12			0	0									
13	0	0	0										
15	8	9	9										
16	3	7	3										
22	8	6	4	6	5	5							
23	0	3	2	3	1								
26	0	5	5										
30	0	0	4	0	6	4	0						
32	2	1	0	6	5	3							
33	0	3	5	0	4	0	0		0	0	0	0	6
40	2	2	6	2	1	2	2	4	2	0			
Measurements nr	12	12	13	8	7	6	3	1	2	2	1	1	

Total measurements 69
Average discomfort level 4.0
SD ±3.3

Table 3.4 – Discomfort levels on the measurement day, number of the measurements and the average discomfort level (± SD) within Active Group

Active subject nr	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
1		9	9								
2	0	2									
4	3	5	0	0							
7	0	1	7	5	1	1					
8	1	1	1								
9	6	2	0	0	0	0	0	0			
10	10	10	5	10	10	10					
11	5	0									
14	4	2	2	1	2	1					
17		2	0								
18	0	0	5	5							
19	3	3	3	4	2	2					
20	4	0	0	0	0	0					
21	5	0	1	0	0						
24	0	0	0	0	0	0					
25		7	7	6	8	5	4	3	3	3	
27	0	2	2								
28	0	0	0	1	1	1					

Active subject nr	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
29	7	3	3	2	2	1	2				
31	6	6	6	5	4	5					
34	10	1	1								
35	10	3	3	10	5						
36	4										
37	0	0	3	0	0						
38	0	8		5							
39	1	0	1	1							
Measurements nr	23	25	22	18	14	11	3	2	1	1	

Total measurements 120
Average discomfort level 2.8
SD ±3.0

The above tables 3.3. and 3.4 show that mean discomfort parameter for Control Group was 4.0 in comparison to the Active Group's mean discomfort parameter which was 2.8. This is a reduction by 30% of discomfort in favor for Active Group with statistical significance of presented p-value result of two sided student t test p=0.01

Table 3.5 – Spasm levels on the measurement day, number of the measurements and the average spasm level (± SD) within Control Group

Control subject nr	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
5	10	6	4	2	3	3							
6	2	0	0										
12			0	0									
13	0	0	0										
15	9	9	9										
16	10	8	6										
22	8	0	2	0	2	0							
23	0	3	2	3	1								
26	0	0	0										
30	10	0	6	0	7	6	2						
32	0	0	3	2	5	7							
33	0	3	0	0	5	4	0		0	0	10	3	4
40	2	0	0	1	0	0	0	0	0				
Measurements nr	12	12	13	8	7	6	3	1	2	1	1	1	

Total measurements 68
Average spasm level 3.6
SD ±3.2

Table 3.6 – Spasm levels on the measurement day, number of the measurements and the average spasm level (± SD) within Active Group

Active subject nr	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
1		0	8								
2	0	0									
4	1	4	0	0							
7	0	0	0	0	0	0					
8	1	1	1								
9	0	0	0	0	0	0	0	0			
10	7	10	5	1	1	0					
11	0	0									
14	0	0	0	0	0	0					
17		0	8								
18	2	0	1	1							
19	0	1	0	2	5	3					
20	10	7	8	5	10						
21	0	0	0	0	0						
24	0	0	0	0	0	0					
25		0	0	0	0	0	0	0	0	3	
27	1	0	0								
28	0	0	0	0	0	0					
29	0	0	0	0	0	0	0				
31	7	7	5	3	1	2					
34	4	0	8								
35	9	8	6	5	6						
36	0										
37	0	0	0	0	1						
38	3	0	2	2							
39	0	0	0	1							
Measurements nr	23	25	23	18	14	10	3	2	1	1	

Total measurements	120
Average spasm level	2.5
SD	±2.7

The above tables 3.5 and 3.6 show that mean spasm parameter for Control Group was 3.6, in comparison to the Active Group's mean spasm parameter which was 2.5 , which is a reduction by 32% in favor for Active Group with statistical significance of presented p-value result of two sided student t test p=0.02.

13 Using of Pain Relief Medication with and without UroShield

85% patients from control group and 63% patients from active group have got pain and spasm medications (11 patients from Control Group and 17 patients from Active Group). The two groups are similar in mean medication strength: 3.7 for Control Group and 3.3 for Active Group

– see tables attached: Table 6 - medications rank, Tables 7-10 mean medication strength for each group.

Furthermore, pain relief medications given to the patients were related not only to pain and discomfort associated with indwelling urinary catheter but rather to pain associated with invasive surgery treatment, therefore pain medications cannot serve as a measurement for the efficacy of the UroShield in this clinical trial because the type and severity of the surgery have a stronger influence on the use of these medications.

14 Bacteriuria Rate with and without UroShield

The bacteriuria levels within the two groups by visit day is presented in table 4. Additionally, the table includes p-values for Fisher's exact test for the comparison of distributions between the Active and Control groups at each visit day.

Table 4 – Bacteriuria levels, active vs. control group

Measurement day	Control						Active						P-value
	No		Yes		All		No		Yes		All		
	N	%	N	%	N	%	N	%	N	%	N	%	
Day 0	12	80.0	3	20.0	15	100.0	26	92.9	2	7.1	28	100.0	0.32
Day 3	9	90.0	1	10.0	10	100.0	18	94.7	1	5.3	19	100.0	0.33
Day 6	4	100.0		0.0	4	100.0	2	50.0	2	50.0	4	100.0	0.42
Day 9	2	100.0		0.0	2	100.0	2	100.0		0.0	2	100.0	N/A
Day 12	1	100.0		0.0	1	100.0							N/A
Total *	16	94.1	1	5.9	17	100.0	22	88.0	3	12.0	25	100.0	0.63

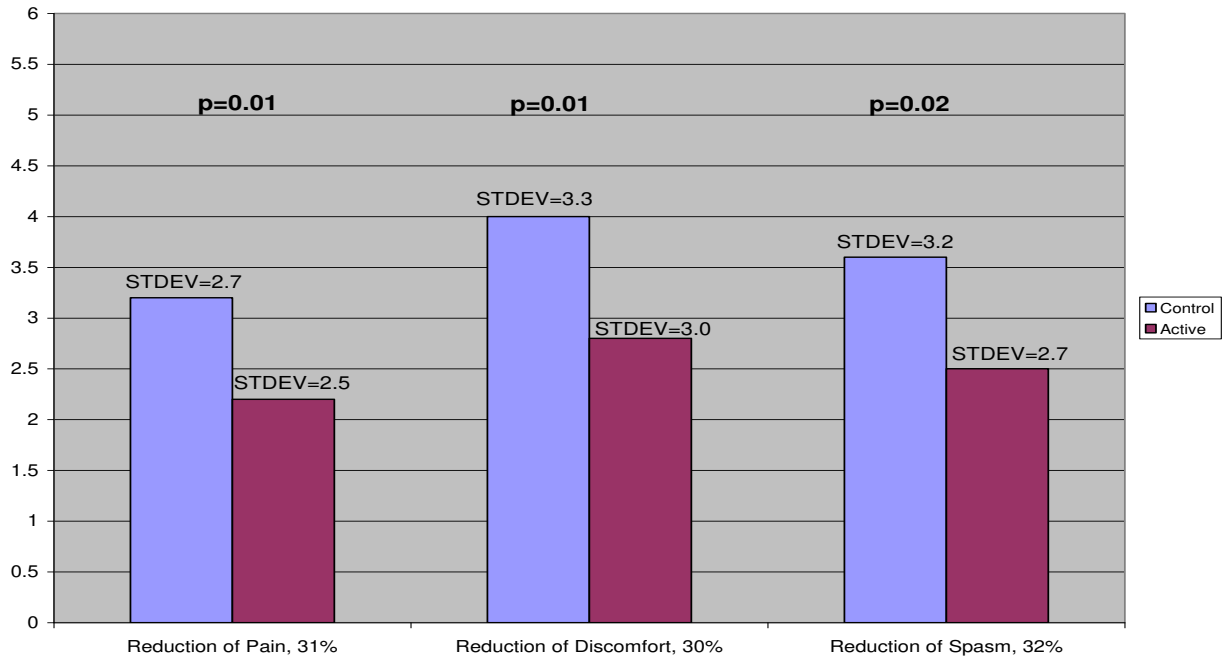
The results show that the rate of bacteria was 5.3% in the Active Group vs. 10.0% in the Control Group for Day 3. The number of subjects from day 6 and onward is insufficient for estimating the rate of bacteria.

15 Discussion

The study groups, the Active Group and the Control Group, were similar in terms of physical and medical parameters. . In terms of safety, there were similar numbers of adverse events in both groups all classified as unrelated to the device.

In terms of efficacy, the study shows evidence that UroShield accessory reduces pain, discomfort and spasm related to urinary catheter usage due to acoustic lubrication which is created on the surface of the urinary catheter through UroShield actuator. The efficacy exploration included data tables for each patient over time and a graphical manner exhibiting the median pain, spasm and discomfort data for treatment (active) and control groups, as it is visualized in the Graph 1 here above.

Graph 1 – Reduction of mean pain, discomfort and spasm levels - control group in comparison to the treatment (active) group, based on the data from the tables 3.1 -3.6



The sample number for some endpoints such as presence of Clinically Significant UTI, and presence of Bacteriuria was insufficient, therefore further clinical evaluation should be conducted to prove that UroShield device is effective in reducing bacteria rate.

It was found that fewer patients were given pain relief medication in the Active Group (57%) versus the Control Group (85%), as it is shown in attachment Table 8 and Table 10. Mean medication strength was in favor of the Active Group (3.3 versus 3.7), see the same tables.

It should be mentioned, that pain relief medications given to the patients were related not only to pain and discomfort associated with indwelling urinary catheter but rather to pain associated with invasive surgery treatment. Pain medications cannot serve as a measurement for the

efficacy of the UroShield in this clinical trial because the type and severity of the surgery have a stronger influence on the use of these medications.

16 Conclusions

- The results of this randomized, controlled study demonstrate that: The Uroshield device is effective in reducing post operative catheter related pain, discomfort and bladder spasms. Reduction in the pain, discomfort and spasm parameters were recognized in favor to the Active Group when was analyzed for each parameter : the severity of pain was reduced by 31%, discomfort by 30% and spasm by 32% in Active Group as a result of UroShield accessory usage. This difference was found to have statistical significance (two-tailed Student t test was used, $p < 0.05$) when comparing Control and Active Groups.
- The trend in reduction of pain, discomfort and spasm mean parameters was recognized in favor to the Active Group for all treatment days (see attachment Table 5).
- 85% patients from control group and 57% patients from active group received pain and spasm relief medications. Comparison of pain and spasm relief medications strength was in favor of the Active Group: 3.7 in Control Group versus 3.4 in Active Group.
- There is a notable trend towards reduction of bacteriuria. Urine cultures on 3rd day revealed bacteriuria in only 5.3% patients with Uroshield compared to 10% in the control patients Group.
- In summary, this randomized, controlled clinical study shows that UroShield accessory is safe, well tolerated, and effective for its intended use..

17 References

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18 Attachments

Table 5 – Mean pain, discomfort and spasm levels for each treatment day

Measurement	Measurement day / Treatment Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
Pain	Control	3.0	3.3	3.2	2.1	3.3	2.5	0.7	4	1	0	0	0	6
	Active	2.2	2.9	2.0	2.2	1.9	1.4	0.8	1	0.5	0.5	0		
Discomfort	Control	4.7	4.9	3.6	3.1	3.4	3.5	2.7	4.0	3.7	0	0	0	6
	Active	3.3	2.6	2.6	2.9	2.3	2.2	1.5	1.0	1.5	1.5	0	0	
Spasm	Control	2.6	2.1	2.3	0.9	3.3	3.3	0.7	0	0	0	0	3	4
	Active	1.9	1.5	2.2	1.1	1.6	0.5	0	0	0	1.5	0		

Table 6 – Medication Ranks

Medications given for pain reduction	Dosage	Rank
PARACETAMOL	1 GR	1
DICLOFENAC SODIUM	75 MG	2
IBUPROFEN	400 MG	3
DIPYRONE	500 MG	4
	1 GR	5
	2 GR	6
	3 GR	7
OXYCODONE HYDROCHLORIDE	5 MG	8
	15 MG	9
	20 MG	10
TRAMADOL	50 MG	11

Medications given for pain reduction	Dosage	Rank
	100 MG	12
	200 MG	13
OXYCODONE+PARACETAMOL	5 G	14
MORPHIN SULPHATE	20 MG	15
PHENERGAN	25 MG	16
PETHIDINE	75 MG	17
DOLESTINE	150 MG	18
	100 G	19

Note: Ranks are in a scale of 1 to 19, where 19 indicates the strongest pain medication. If a patient received more than one pain relief medication per day, the ranks of these medications were summarized.

Table 7 – List and rank of the Medications per patient for Control Group

Subject nr	Visit Day	Medication	Dose	X medication rank
5	Day 1	PETHIDINE	75 MG	17
5	Day 2	DIPYRONE	1 GR	5
6	Day 1	DIPYRONE	500 MG	4
12	Day 2	MORPHIN SULPHATE	20 MG	15
12	Day 3	PARACETAMOL	1 GR	1
13	Day 1	DIPYRONE	1 GR	5
13	Day 2	DIPYRONE	2 GR	6
13	Day 2	PETHIDINE HCL	75 MG	17
13	Day 3	DIPYRONE	1 GR	5
16	Day 1	DIPYRONE	1 GR	5
16	Day 1	OXYCODONE HYDROCHLORIDE	5 MG	14
16	Day 2	DIPYRONE	3 GR	7
16	Day 2	OXYCODONE HYDROCHLORIDE	20 MG	15
16	Day 3	DIPYRONE	2 GR	6
16	Day 3	OXYCODONE HYDROCHLORIDE	15 MG	9
22	Day 2	DIPYRONE	2 GR	6
26	Day 1	DIPYRONE	1 GR	5
30	Day 4	DIPYRONE	1 GR	5
32	Day 1	PERCOCET	5 MG	1
32	Day 1	PERCOCET	5 MG	1
32	Day 2	TRAMADOL	100 MG	12
33	Day 2	PETHIDINE	75 MG	17
40	Day 1	DIPYRONE	1 GR	5

Subject nr	Visit Day	Medication	Dose	X medication rank
40	Day 4	TRAMADOL	100 MG	12
40	Day 6	IBUPROFEN	400 MG	3

Note: Only medications, which were counted for presentation of the Pain Relief Medication Ranks table, are presented.

Table 8 – Medication strength for Control group

Subject/day	1	2	3	4	5	6	7	8	9	10	11	12	13
5	17	5	0	0	0	0							
6	4	0	0										
12			15	1									
13	5	23	5										
15	0	0	0										
16	19	22	13										
22	0	6	0	0	0	0							
23	0	0	0	0	0								
26	5	0	0										
30	0	0	0	5	0	0	0						
32	2	12	0	0	0	0							
33	0	17	0	0	0	0	0	0	0	0	0	0	0
40	5	0	0	12	0	3	0	0	0	0			

Measurement nr. 70
Mean med. Strength 3.7
patients with pain relief drugs 85%

Table 9 – List and rank of the Medications per patient for Active Group

Subject Nr	Visit Day	Medication	Dose	X medication rank
1	Day 1	PHENERGAN	25 MG	16
1	Day 1	PETHIDINE	75 MG	17
1	Day 2	DIPYRONE	1 GR	5
2	Day 1	OPTALGIN	1 GR	1
2	Day 1	PHENERGAN	25 MG	16
4	Day 1	DIPYRONE	1 G	5
4	Day 4	DICLOFENAC SODIUM	75 MG	2

Subject Nr	Visit Day	Medication	Dose	X medication rank
9	Day 2	GRAUK DIPYRONE	1 GR	5
9	Day 3	DIPYRONE	2 GR	6
9	Day 6	DIPYRONE	1 GR	5
9	Day 7	DIPYRONE	3 GR	7
9	Day 8	DIPYRONE	1 GR	5
10	Day 2	DIPYRONE	2 GR	6
10	Day 3	DIPYRONE	1 GR	5
10	Day 3	OXYCODONE+PARACETAMOL	5 G	8
10	Day 3	OXYCODONE+PARACETAMOL	5 G	8
10	Day 3	DOLESTINE	100 G	19
10	Day 6	DIPYRONE	1 GR	5
17	Day 2	DIPYRONE	1 GR	5
19	Day 2	DIPYRONE	1 GR	5
19	Day 4	DIPYRONE	2 GR	5
20	Day 1	DOLESTINE	150 MG	18
20	Day 4	DIPYRONE	1 GR	5
20	Day 5	DOLESTINE	75 MG	9
20	Day 6	DIPYRONE	2 GR	6
24	Day 2	DIPYRONE	1 GR	5
24	Day 4	DIPYRONE	1 GR	5
24	Day 5	DIPYRONE	2 GR	6
29	Day 1	DIPYRONE	2 GR	6
29	Day 1	PERCOCET	5 MG	1
29	Day 1	PERCOCET	5 MG	1
29	Day 1	TRAMADOL	100 MG	12
29	Day 5	TRAMADOL	200 MG	13
31	Day 1	DIPYRONE	1 GR	5
31	Day 2	PERCOCET	5 MG	1
31	Day 2	PERCOCET	5 MG	1
31	Day 3	DIPYRONE	1 GR	5
31	Day 4	DIPYRONE	2 GR	6
31	Day 5	DIPYRONE	1 GR	5
34	Day 1	DIPYRONE	1 GR	5
34	Day 2	PERCOCET	5 MG	1
34	Day 2	PERCOCET	5 MG	1
37	Day 1	DIPYRONE	2 GR	6
37	Day 4	DIPYRONE	1 GR	5
38	Day 2	DIPYRONE	1 GR	5

Subject Nr	Visit Day	Medication	Dose	X medication rank
39	Day 1	DIPYRONE	1 GR	5
39	Day 4	DIPYRONE	2 GR	6

Note: Only medications, which were counted for presentation of the Pain Relief Medication Ranks table, are presented.

Table10 – Medication strength for Active Group

Subject/day	1	2	3	4	5	6	7	8	9	10	11
1	33	5	0								
2	1	16									
4	5	0	0	2							
7	0	0	0	0	0	0					
8	0	0	0								
9	0	5	6	0	0	5	7	0			
10	0	6	40	0	5	0					
11	0	0									
14	0	0	0	0	0	0					
17	0	5	0								
18	0	0	0	0							
19	0	5	0	5	0	0					
20	18	0	0	5	9	6					
21	0	0	0	0	0						
24	0	5	0	5	6	0					
27	0	0	0								
28	0	0	0	0	0	0					
29	20	0	0	0	0	0	0				
31	5	2	5	6	5	0					
34	5	2	0								
35	0	0	0	0	0						
36	0										
37	6	0	0	0	0						
38	0	5	0	0							
39	5	0	0	6							

Measurement nr. 120
Mean med. strength 3.3.
Patients with pain relief medication 57%

ATTACHMENT: Report Signature Page

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