MULTICENTRE, CONTROLLED, RANDOMIZED CLINICAL TRIAL TO ASSESS THE EFFICACY AND COST-EFFECTIVENESS OF URINARY CATHETERS WITH SILVER ALLOY COATING VERSUS CONVENTIONAL CATHETERS IN SPINAL CORD INJURED PATIENTS.

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1. Abstract of the original project

Objectives: the general objective of the study was to compare the incidence of urinary tract infections due to the use of antiseptic silver alloy-coated silicone urinary catheters with the incidence of urinary tract infections due to the use of conventional urinary catheters in patients with spinal cord injury (SCI).

Design: multicentre, international, randomised, open clinical trial with a healthcare device, parallel groups and blinded assessment of the primary outcome. Phase IV trial of a healthcare device authorized in the European Community in the approved conditions of use. Rehabilitation centres were included.

The study was submitted to the consideration of the relevant Clinical Research Ethics Committee of each centre. All patients were informed about the study and signed the informed consent.

Interventions: the study assessed the use of antiseptic silver-alloy-coated silicone urinary catheters (experimental intervention) and the use of urinary catheters commonly used in the research centre (mostly silicone) (conventional catheters (control intervention)). The duration of the intervention was from the moment of urethral catheterisation (for the first time or as a replacement of an indwelling catheter) until a new replacement (usually within 30 days) or removal. The decision about when to remove or replace was a clinical judgement.

Inclusion criteria were adult patients (aged 18 or over) of either sex, with traumatic or medical SCI needing an indwelling urinary catheter as a method of bladder drainage.

Randomisation: a computer generated a table with random numbers, stratified by centre. The randomisation was centralised using an electronic platform with a secure access through the website. Neither the researcher nor any collaborator nor the patient knew in advance the allocation to the intervention.

Study outcomes:

Primary outcome: development of a UTI related to urinary catheterization. A patient was considered to suffer UTI if they presented a positive urine culture (to no

more than two uropathogens) in the context of clinical signs. UTI was considered to be catheter-associated when the urine sample was obtained within 30 days after the urethral catheterisation or before its replacement or removal.

Secondary outcomes: septicaemia, adverse events and costs.

Data collection: all the information required by the protocol during the trial was entered in an electronic data capture system with restrained and secure web access (http://www.ensayoescale.com/ for the centres in Spain and Chile; http://en.ensayoescale.com/ for the European centres).

2. Results

The patient recruitment period went from September 2012 to November 2015. A total of 512 patients were recruited, and 493 were randomized: 475 in Spain, 6 in Chile, 9 in Portugal, 3 in Turkey, and 1 in Italy. A total of 247 patients were allocated to the silver-alloy-coated urinary catheter or experimental group, and 246 to the conventional urinary catheter or control group (Figure 1).

The baseline characteristics of randomised patients are summarised in Table 1 and show a similar distribution between both groups, with no significant differences. In general, the study population included men (74%) aged 55 to 57. Hospitalised patients represented 43% and the rest were outpatients. The most frequent level of SCI was cervical spine (42%) and the most frequent cause was trauma (73%). Most of them had an A score on ASIA scale (62%). Mean time of urethral catheterisation before study inclusion was 48 (SD 77) months.

In the sample of included patients, 64 (13%) patients were randomised more than once to the study, after at least a month since termination of the participation. A total of 29 (12.1%) were randomised to the silver alloy-coated urinary catheter and 35 (14.6%) to the conventional urinary catheter group.

A total of 493 of the randomised patients received a urinary catheter; 247 received the

silver urinary catheter and 246 the conventional urinary catheter. Antibiotic prophylaxis was allowed in the study according to each centre's policy. Thus, 91 patients of the experimental group and 93 of the control group received antibiotic prophylaxis prior to the urethral catheterisation (p = 0.998).

The mean time of urethral catheterisation with the study urinary catheter was 23 days (SD 10.18) in the experimental group and 25 days (SD 10.50) in the control group (p = 0.073).

Urinary catheter was replaced in 186 (79.1%) patients in the experimental group and 195 (80.2%) in the control group and it was removed from the rest definitively (p = 0,427). The most common reason of the urinary catheter replacement was compliance with the 30-day period with urinary catheter, and the most common reason for removal was changing to a different bladder drainage system.

Table 1. Baseline characteristics of randomised patients

	Silver-alloy-coated urinary catheter (N = 247)	Conventional urinary catheter (N = 246)	p
Age (mean and standard deviation) (years)	55.00 (16.53)	57.00 (16.56)	0.184
Sex (male) (no. of patients and %)	178 (72.00)	188 (77.00)	0.256
Inpatients (no. of patients and %)	108 (44.00)	106 (43.30)	0.603
Time of urethral catheterisation (mean and standard deviation) (days)	44.54 (65.28)	50.54 (88.54)	0.405
Aetiology of the SCI (no. of patients and %)			
Traumatic	175 (74.20)	177 (73.10)	0.440
Medical	62 (25.80)	65 (26.90)	
Level of injury C1_C8	109 (45.20)	100 (40.70)	0.110
Level of injury D1_D9	74 (30.70)	73 (29.70)	
Level of injury D10_L1	44 (18.30)	65 (26.40)	
Level of injury L2_L5	14 (5.80)	8 (3.30)	
ASIA Scale (no. of patients and %)			
A (No sensory or motor function is preserved in the sacral segments S4-S5.)	158 (65.80)	148 (61.40)	0.614
B (Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 and no motor function)	31 (12.90)	29 (12.00)	
C (Motor function is preserved below the neurological level, and more than half of key muscle functions below the neurological level of injury (NLI) have a muscle grade less than	35 (14.60)	44 (18.30)	
D (Motor function is preserved below the neurological level, and at least half of key muscle functions below the NLI have a muscle grade of 3 or over)	16 (6.7)	19 (7.90)	
E (Sensation and motor function are	0	1 (0.40)	
Diabetes (Type 1 and 2) (no. of patients and %)	26 (11.00)	43 (18.20)	0.090
Radiation Therapy (no. of patients and %)	5 (2.10)	2 (0.80)	0.282
Chemotherapy (no. of patients and %)	3 (1.20)	2 (0.80)	-
Corticosteroids (no. of patients and %)	5 (2.10)	7 (2.80)	0.772

Urinary tract infection:

In the intention-to-treat analysis (considering all randomised patients), 41 patients of the silver-alloy-coating urinary catheter and 42 of the conventional urinary catheter had suspected UTI (p = 1.000).

Suggestive symptoms and/or signs of UTI were observed in 45 patients of the experimental group and 37 in the control group. The most common were changes in urine characteristics.

Out of the patients with symptoms and/or signs suggesting UTI, 15 patients of the experimental group and 20 of the control group had a positive urine culture to only one pathogen. The most common organisms were *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Proteus mirabilis.*

Six patients of the experimental group and five of the control group had a positive urine culture to two organisms, with no significant differences between the groups. Only one blood culture of the experimental groups and two of the control group were positive.

Septicaemia with urinary origin:

Two septicaemias with urinary origin occurred, one in each intervention group. See adverse events.

Adverse events:

Thirteen patients of the experimental group and nine of the control group presented an adverse event. Adverse events appear on the following list:

No of patients

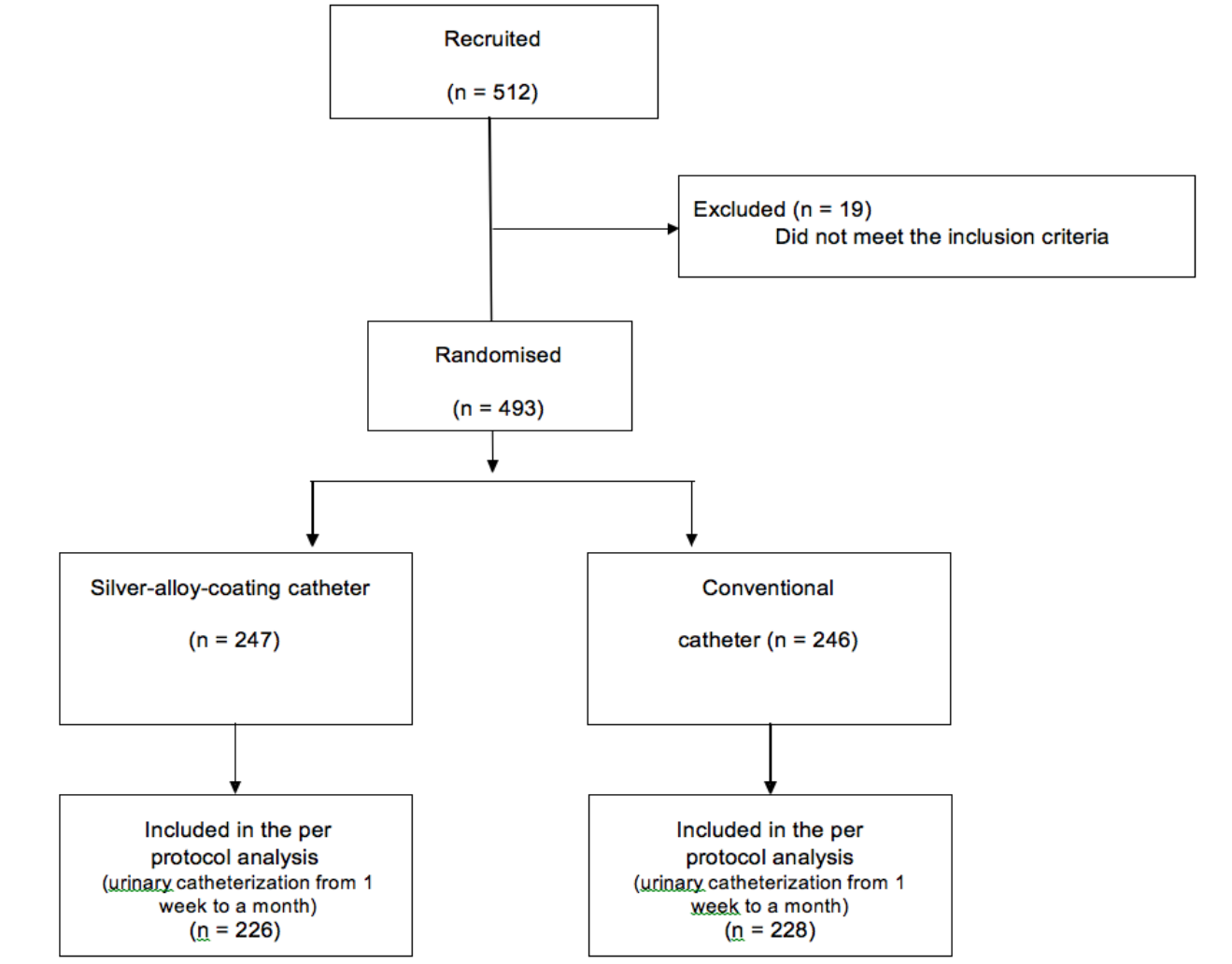
- Non-focused febrile syndrome 1
- Catheter obstruction 2
- Bladder and urethral itching 1
- Calcaneal osteomyelitis 1
- Hospital admission due to disease 1
- UTI previous to catheterisation 1
- Surgical wound infection 1
- Wound in urethral meatus 3
- Urine leakage around the 2
- Pruritic rash 1
- Headache and itching 1
- Suprapubic pain 1
- Pulmonary thromboembolism 1
- Septicaemias with urinary 1
- Septic shock 1
- Death 3

During the study, 6 patients presented a serious adverse event, 3 of which were death: an 85 year-old woman allocated to the silver-alloy-coating urinary catheter, and two men of 78 and 79 allocated to the conventional group. No death was related to the urinary catheter. Another four adverse events were serious although not lethal and were solved: one was a pulmonary thromboembolism non-related to the silver alloy-coating urinary catheter, two were septicaemias with likely or potential urinary origin (one in each intervention group), and one was exacerbated with septic shock (in the silver alloy-coating group; possible causality relation). Another serious adverse event was hospital admission non-related to the urinary catheter of a 63 year-old man presenting other co-morbidities.

Cost study:

Despite the design of the protocol and an analysis plan to conduct a cost-effectiveness study, due to the lack of significant differences in all clinical results, the cost-effectiveness analysis was not conducted.

Figure 1. Study patients flow diagram



3. Relevance and potential clinical implications of the obtained final results

The clinical trial has an adequate patient sample to identify clinically relevant differences between both urinary catheters. These differences appear to be minimal and non-significant. Given that the silver-alloy-coated urinary catheters have a far higher cost than conventional catheters, the finding of the study is relevant.

The interest of this study consists in providing useful information to clinicians and managers about efficacy and safety of silver alloy-coated urinary catheters in relation to conventional catheters.

Given the large number of patients included in the study, the dissemination of the results will reveal that further studies on these patients are not required.

4. Publications or communications from this research

1. The trial protocol was registered in the National Library of Medicine (NLM) database clinicaltrials.gov, including information about the methods of clinical trials and the main results once it is completed. The references can be found at www.clinicaltrials.gov using the code: **NCT01803919.**

Furthermore, the study protocol was published in an open-access journal attached, and its references are:

2. Bonfill X, Rigau D, Jáuregui-Abrisqueta ML, Barrera Chacón JM, Salvador de la Barrera S, Alemán-Sánchez CM, Bea-Muñoz M, Moraleda Pérez S, Borau Duran A, Espinosa Quirós JR, Ledesma Romano L, Esteban Fuertes M, Araya I, Martínez-Zapata MJ. ***A randomized controlled trial to assess the efficacy and cost-effectiveness of urinary catheters with silver alloy coating in spinal cord injured patients: trial protocol.*** *BMC Urol. 2013;13(1):38.*