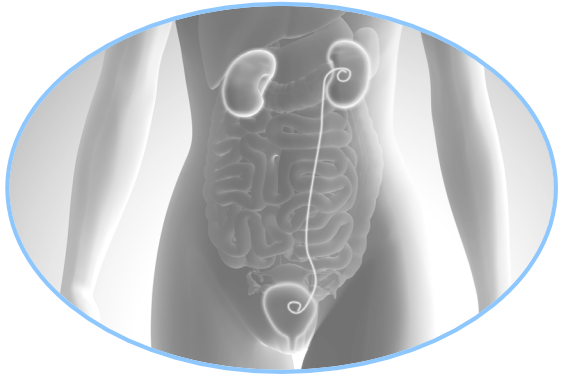
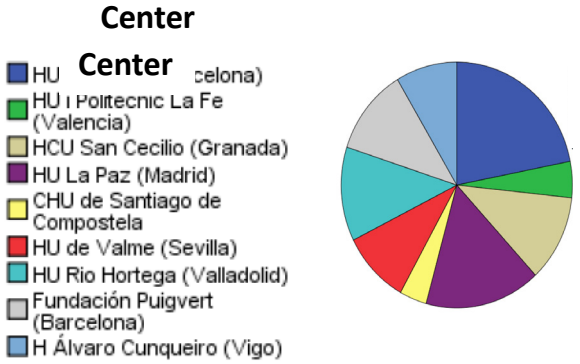
A MULTICENTRIC RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE COMBINED USE OF A MEDICAL DEVICE AND A FOOD SUPPLEMENT IN CONTROLLING THE URINARY pH IN PATIENTS WITH AN INDWELLED DOUBLE J STENT



Recruiting hospitals, patients and disclosure

Hospital / Investigator	City	Total recruited patients
Hospital Universitari de Bellvitge	Barcelona	23
Hospital Universitari i Politècnic La Fe	Valencia	5
Hospital Clínico Universitario San Cecilio	Granada	12
Hospital Universitario La Paz	Madrid	17
Complejo Hospitalario Universitario de Santiago de Compostela	Santiago de Compostela	4
Hospital Universitario de Valme	Sevilla	10
Hospital Universitario Rio Hortega	Valladolid	13
Fundació Puigvert	Barcelona	12
Hospital Álvaro Cunqueiro	Vigo	9
Total		**105**



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Stents analysis: Dr. Félix Grases y Antonia Costa

Sponsor contact: Jordi Cuñé Castellana, PhD (jcune@devicare.com)

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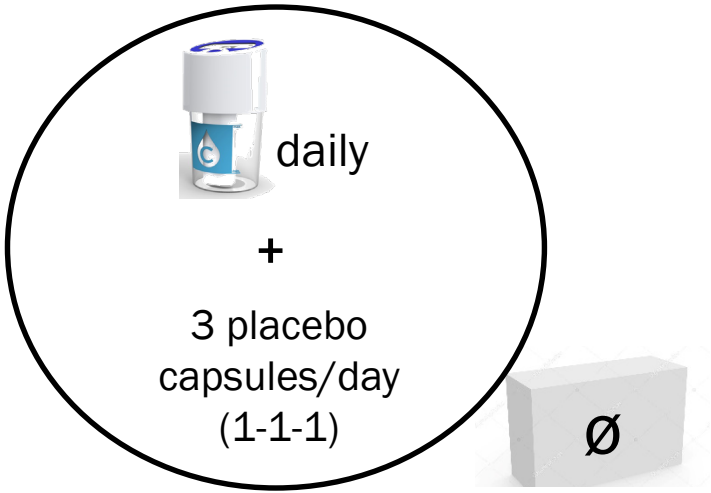
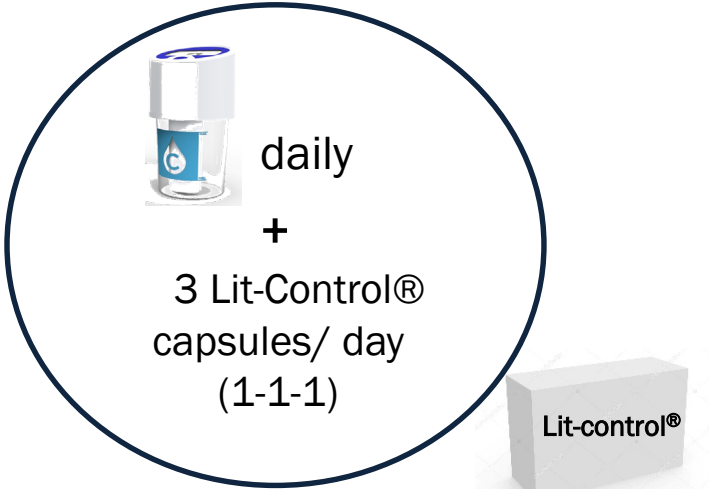
NCT03343275

Groups, administration and patient distribution at baseline

Placebo group = 52



Experimental group= 53



Main objective: Inscrustation

Assess the efficacy of Lit-Control® pH Down in preventing the calcification/incrustation of Double J Stents

- **Measurements of stent ends calcification/incrustation**
  - *i. Stent ends global incrustation (direct score of 3 or exponential of 1.000)*
  - *ii. Deposit levels*

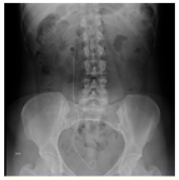
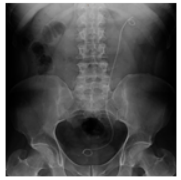
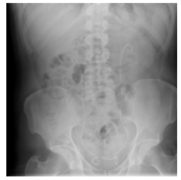
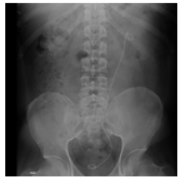
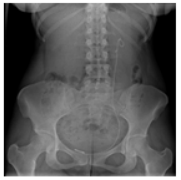
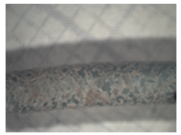
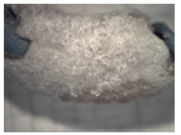
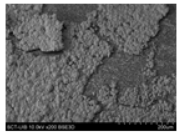
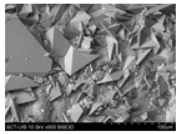
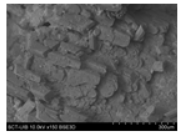
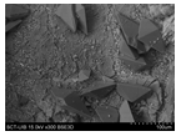
- **Measurements of stent calcification /incrustation**
  - *i. Deposit level at kidney stent end*
  - *ii. Deposit levels at bladder stent end*
  - *iii. Sum of stent ends deposit levels*
  - *iv. Maximum deposit levels*

- **Measurements of stent calcification /incrustation**
  - *i. Presence of bacteria*
  - *ii. Presence of brushite*
  - *iii. Presence of organic matter*
  - *iv. Presence of COM*
  - *v. Presence of COD*
  - *vi. Presence of hydroxyapatite*

Assessment of Double J stents incrustation

- 0 No crystals
- 0 (f) Biofilm
- 1 Few crystals
- 2 Large Crystals
- 3 Global calcification

Encrustation measurement of Double J ureteral stent

Radiographic image					
Macroscopic view					
Electron microscope					
Definition	without inlay		sporadic calcifications	calcifications of wide areas	complete blockage
	0	0 (f)	< 1-2mm^2	> 1-2mm^2	complete blockage
Encrustation score	0		1	2	3
Exp. Score (10^X)	1		10	100	1000

(f) presence of film

Log scale

Results and Conclusions

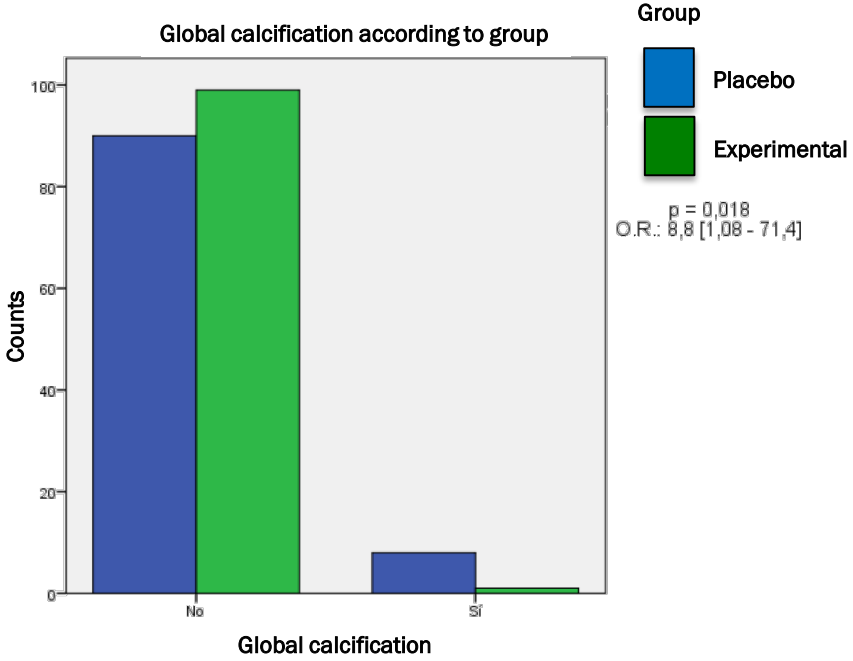
Main objective: incrustation prevention

CONCLUSION #1

After analyzing all stent ends in the placebo group there have been 8 global calcifications (grade 3) and only 1 in the experimental Lit-Control® (O.R: 8,8). This effect increased when multivariate tests were performed adjusted according to age, sex, previous stent implantation, stent composition, duration of implantation and baseline pH at days 1-3.

We can conclude that Lit-Control® decreases more than 8-fold the probability that one stent end will reach global calcification.

Global calcification comparison (value = 3) between groups for the totality of Double J stent ends



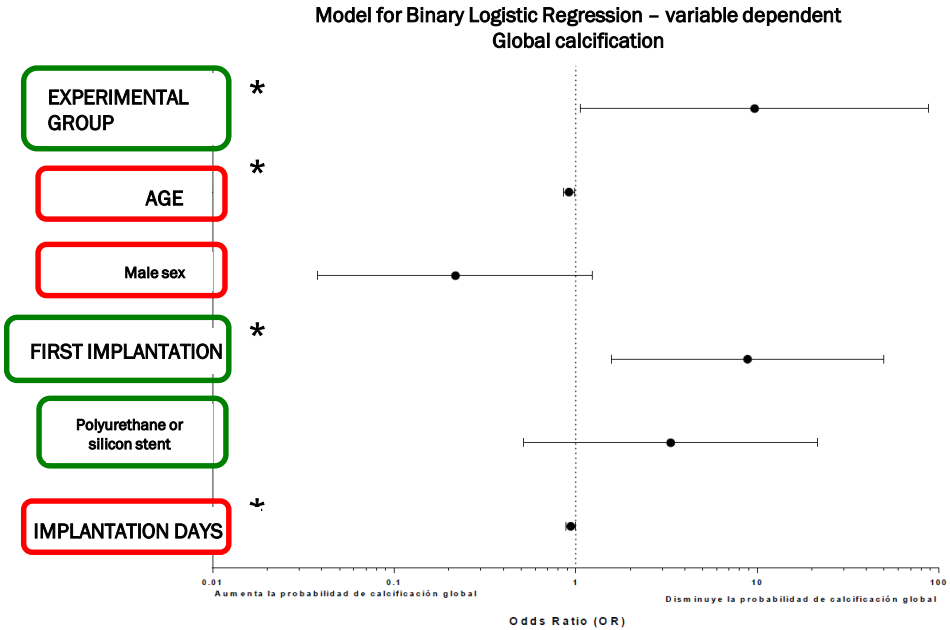
Global calcification comparison according to groups for the totality of Double J stent ends (n= 198)

		Placebo		Experimental		Total		Inference		
		N	%	N	%	N	%	OR	IC95% OR	p-Fisher
Global calcification	No	90	91,8	99	99	189	95,5	8,8	1,08 – 71,4	0,018
	Y	8	8,2	1	1,0	9	4,5			
	Total	98	100,0	100	100,0	198	100,0			

i. We observe a statistically significant difference in the number of stent ends affected by global calcification (score=3 or 1.000 in log scale). p = 0,018

ii. The obtained OD shows a 8-fold lower probability for incrustation when placed in the experimental group.

Binary logistic regression: **global calcification (value = 3)** for all Double J stent ends



	B	standard error	Wald	gl	Sig.	EXP (B)	95% C.I: for EXP (B)	
							Inferior	Superior
Experimental group	2,269	1,127	4,058	1	**0,044**	9,674	1,063	88,012
Age	-0,085	0,036	5,691	1	**0,017**	0,918	0,857	0,985
Male sex	-1,524	0,887	2,949	1	0,086	0,218	0,038	1,240
First implantation	2,180	0,88	6,130	1	**0,013**	8,842	1,575	49,646
Polyurethane / silicon stent	1,205	0,95	1,610	1	0,204	3,337	0,519	21,642
Implantation days	-0,062	0,032	3,858	1	**0,05**	1,064	1,000	1,132
Constant	-4,839	2,062	5,507	1	0,019	0,008		

Exp(B) = Magnitude of the effect (inhibitor or cause of incrustation)

* Statistically significant Decreases incrustation odds Increases incrustation odds

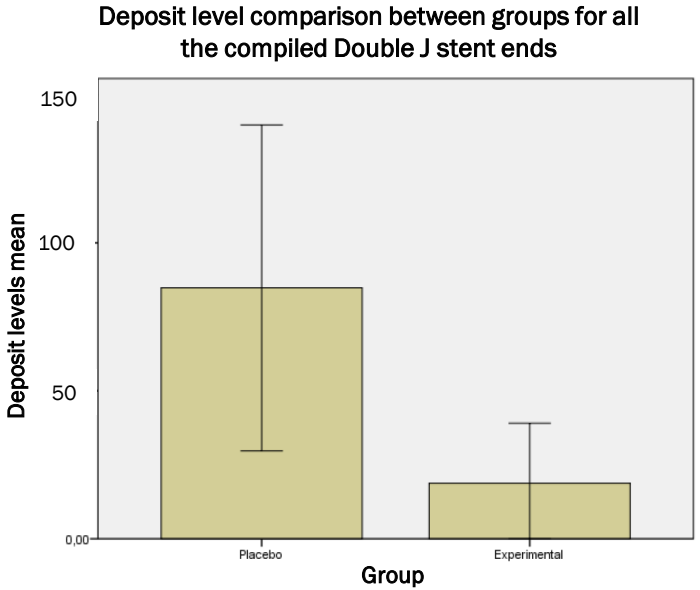
Main objective: incrustation prevention

CONCLUSION #2

As for deposit levels in the analysis, we observed for all stent ends a calcification level of 85,12 (274,5) in the placebo group, while the Lit-Control® group present levels like 18,9 (102,27), with a p= 0,02.

So the experimental treatment proposed significantly reduced deposit levels in Double J stent ends

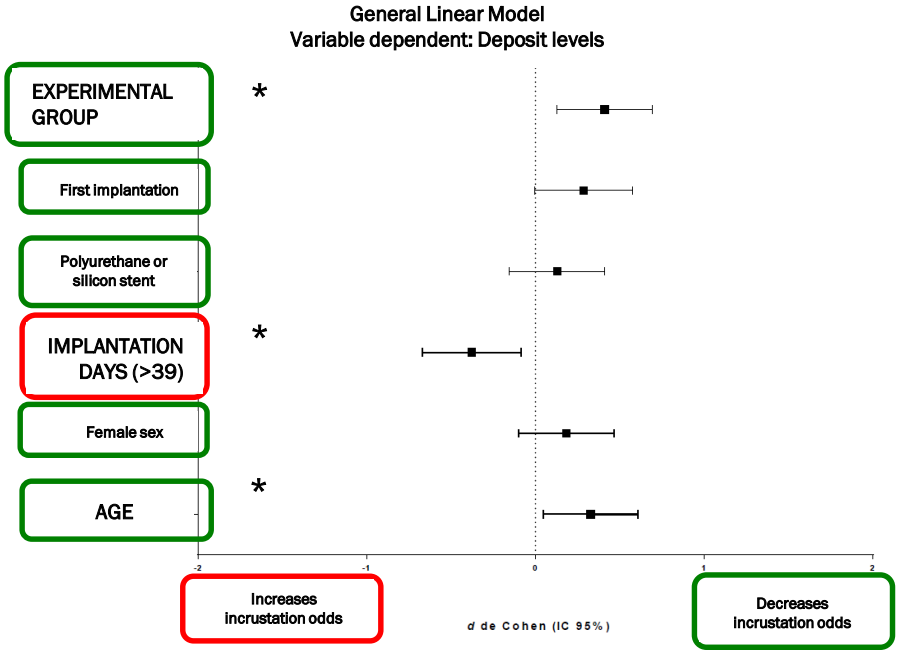
Deposit level comparison of both groups for all Double J stent ends



	Placebo		Experimental		Total		Inferences		
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	*d* Cohen (CI 95%)	p-ANOVA	p-MW
Deposit levels	85,91 (274,5)	98	18,9 (102,27)	100	51,41 (108,5)	198	0,32 (0,04-0,6)	**0,026**	**0,021**

i. We observe a statistically significant difference in incrustation levels considering all stent ends for treatment groups (p =0,026)

General Linear model: **deposit levels** for all Double J stent ends



	F	Sig.	Partial Eta^2
Group	8,243	**0,005**	0,048
First implantation	3,785	0,053	0,022
Stent composition	0,789	0,376	0,005
Implantation days	6,560	**0,011**	0,038
Sex	1,642	0,202	0,010
Age	5,249	**0,023**	0,031

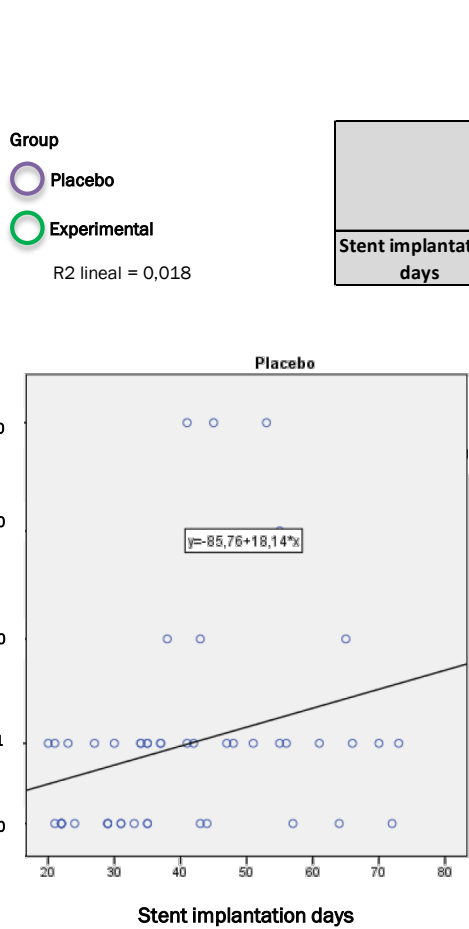
Partial Eta^2= Magnitude of the effect (inhibitor or cause of incrustation)

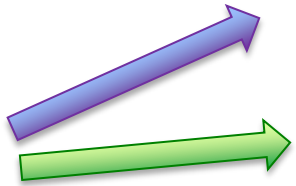
* Statistically significant Decreases incrustation odds Increases incrustation odds

Relation between incrustation and days of stent implantation in the experimental and placebo groups

Table: Correlation between deposit levels and stent implantation days (entire sample)

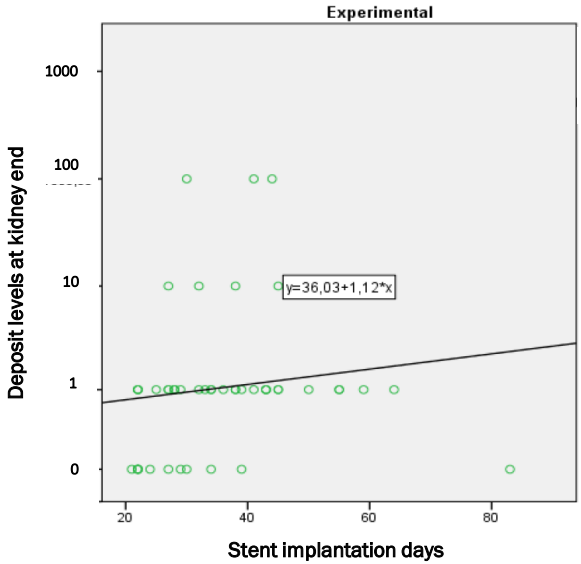
	Deposit levels at kidney end			Deposit levels at bladder end			Sum for stent ends incrustation			Maximum deposits		
	Spearman's Rho	Sig.	N	Spearman's Rho	Sig.	N	Spearman's Rho	Sig.	N	Spearman's Rho	Sig.	N
Stent implantation days	0,345	<0,001	98	0,211	0,037	98	0,28	0,005	98	0,233	0,021	98





Graphs and projections show that the resultant slope counterposing incrustation levels and stent implantation days is less pronounced in the experimental group when compared to placebo.

Lit-Control® confers protection from incrustation associated with the number of days with a stent indwelled.



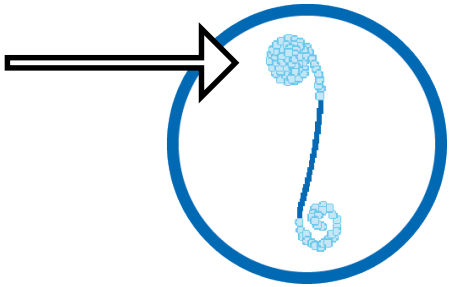
Main objective: incrustation prevention

CONCLUSION #3

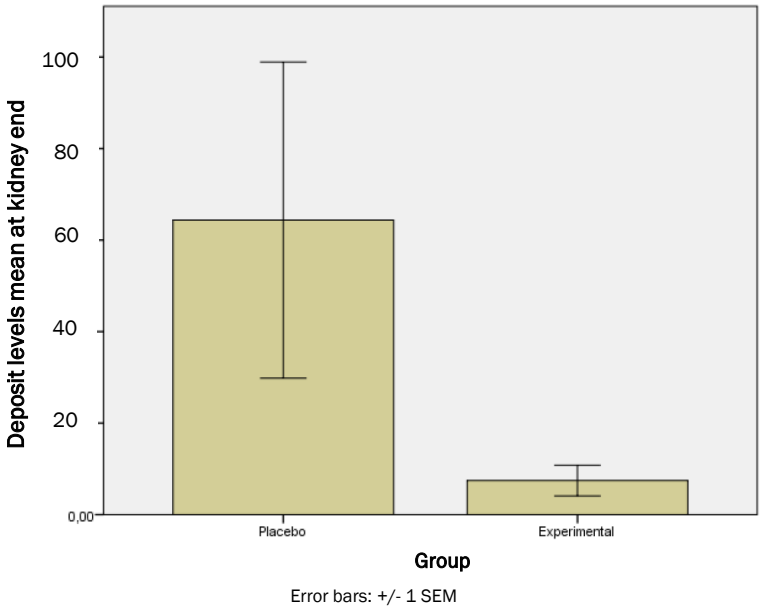
In this incrustation analysis, differentiated by a) deposits at kidney end, b) deposits at bladder end, we can see a reduced incrustation in the experimental group treated with Lit-Control® compared to placebo.

There aren´t statistically significant, but a tendency is demonstrated (p values from 0,05 to 0,2).

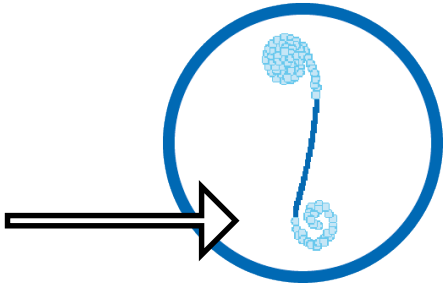
Incrustation/calcification comparison between **groups:** Deposit levels at **kidney end**

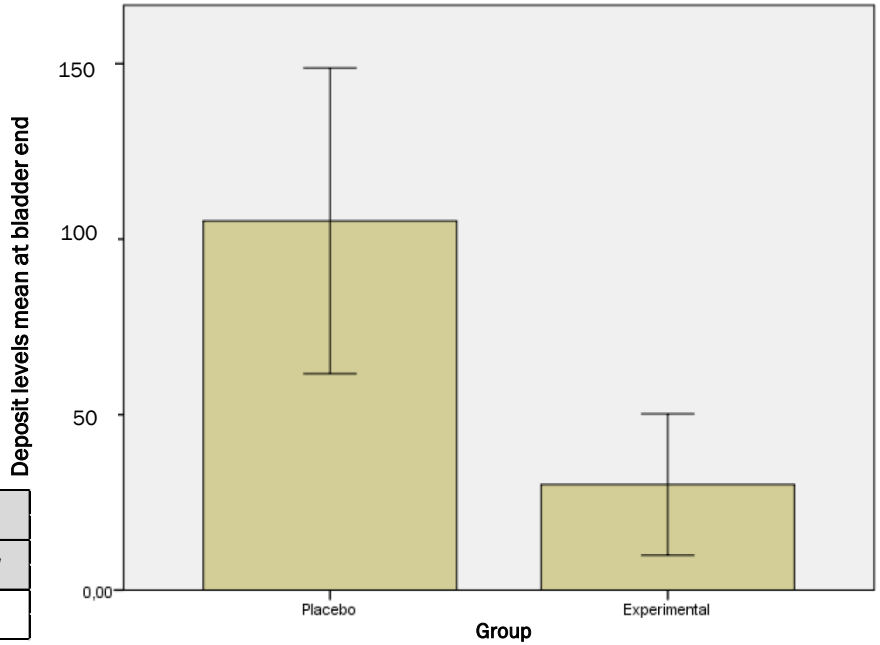


	Placebo		Experimental		Total		Inferences		
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	*d* Cohen (CI 95%)	p-ANOVA	p-MW
Deposit levels at kidney end	64,3 (241,8)	49	7,44 (23,69)	50	36,48 (172,4)	99	0,14 (-0,26-0,53)	0,1	0,20



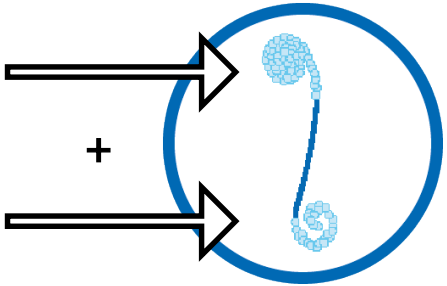
Incrustation/calcification comparison between **groups**: Deposit levels at **bladder end**

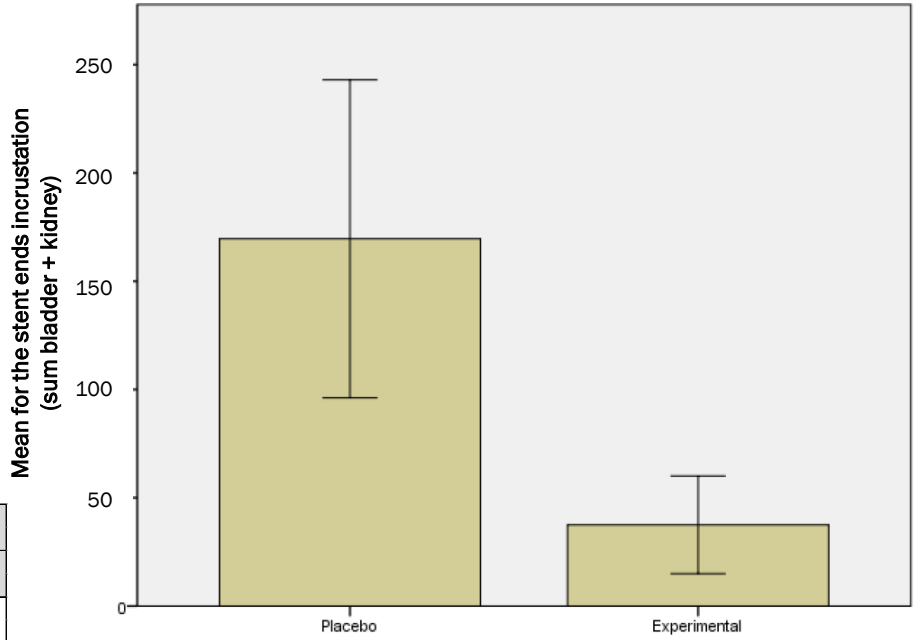




	Placebo		Experimental		Total		Inferences		
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	*d* Cohen (CI 95%)	p-ANOVA	p-MW
Deposit levels at bladder end	105,16 (305,91)	49	30,7 (142,37)	50	67,24 (239,13)	99	0,32 (0,08-0,71)	0,12	>0,05

Incrustation/calcification comparison between **groups: sum** of stent **ends**





	Placebo		Experimental		Total		Inferences		
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	*d* Cohen (CI 95%)	p-ANOVA	p-MW
Deposit levels (sum for bladder and kidney ends)	169,54 (513,8)	49	37,44 (159,08)	50	102,82 (382,57)	99	0,35 (-0,05-0,75)	0,09	0,09

Main objective: incrustation prevention

CONCLUSION #4

The incrustation values for the following: a) deposits detected at the kidney end, b) deposits detected at the bladder end, c) sum for deposits in both stent ends, and d) maximum deposits at both stent ends, were subjected to a multivariate analysis as General Lineal Models in order to adjust the results to population variables and other variables related to the incrustation,

The combination of the 4 incrustation-dependent variables (a-d) with the population and incrustation factors produced 60 General Lineal Models from which 36 are statistically significant for the use of Lit-Control® to drastically reduce stent incrustation. The remaining models show a strong, statistically-significant trend.

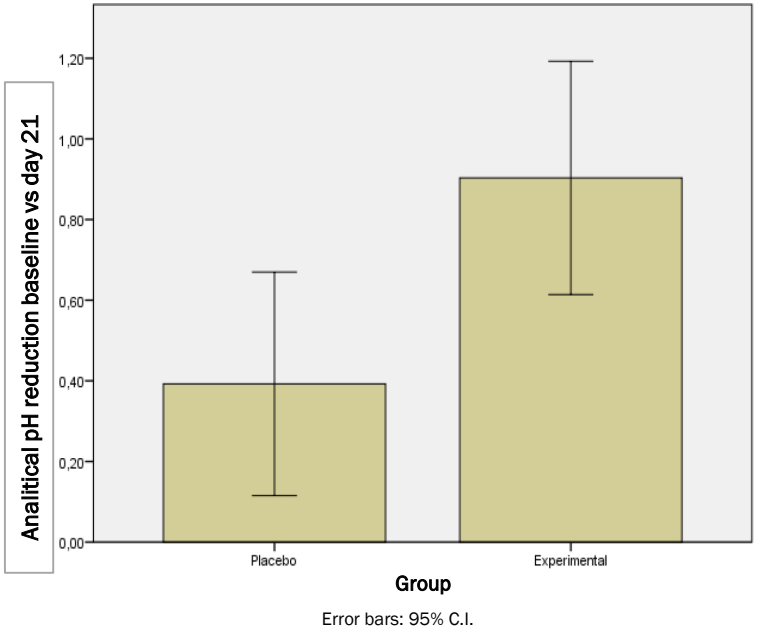
Main objective: incrustation prevention

GLOBAL CONCLUSION

Deposits in Double J stent ends seem to come from a multifactorial process where urinary pH acidification and increase in inhibitory substances with **Lit-Control®** may offer an important prevention.

Secondary objective#1: pH control

CONCLUSION #1



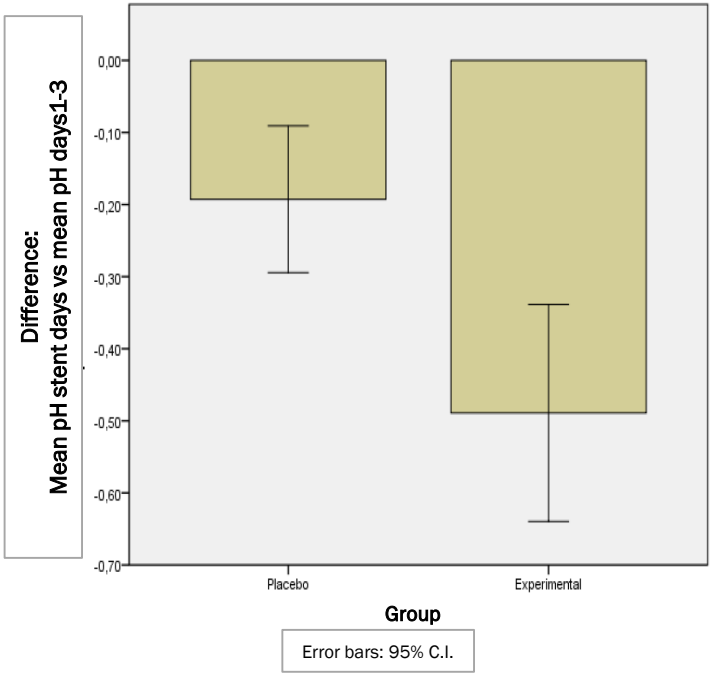
pH values at day 21 vs day 1:

The placebo group showed a 0,39* drop in pH degrees versus a 0,90 decline in the experimental group Lit-Control® (p=0,018)

	Placebo		Experimental		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
pH decrease day1 vs day21	0,39 (0,7)	28	0,9 (0,78)	32	0,64 (0,77)	60	**0,018**	0,08

Secondary objective#1: pH control

CONCLUSION #2



Mean pH values during stent implantation and the mean pH values for days 1-3:

The placebo group showed a drop of -0,2 pH degrees versus a decline of -0,48 in the Lit-Control® group (p=0,002)

	Placebo		Experimental		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
Difference: mean pH stent days vs mean pH days1-3	-0,2 (0,32)	40	-0,48 (0,44)	39	-0,34 (0,41)	79	**0,002**	**0,014**

Secondary objective#1: pH control

GLOBAL CONCLUSION

Globally, we demonstrate here a statistically significant relation between **the pH reduction observed during catheterization and the level of deposits found after catheter removal.**

Secondary objective#2: cost-effectivity

CONCLUSION

During this study, 7 cases of stent removal were impossible in the first attempt , with 5 cases in the placebo group and 2 cases in the Lit-Control® group (p= 0,44).

Mean time for stent removal was 13,8 (30,47) minutes for the placebo group and 7,23 (13,49) minutes for the Lit-Control® group (p= 0,16).

	Placebo		Experimental		Total		Inferences	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	p-ANOVA	p-MW
Stent removal time (minutes)	13,8 (30,47)	52	7,23 (13,49)	52	10,5 (23,68)	104	0,16	0,76

Secondary objective#3: safety

CONCLUSION #1

Lit-Control® was tolerated as well as the placebo treatment, registering 3 adverse reactions for the placebo group and 3 for the experimental group. No correlation between these adverse events and the product we used could be demonstrated.

It was observed that 71% of the patients had taken more than 80% of the prescribed doses. There was no negative correlation between adherence and efficacy.

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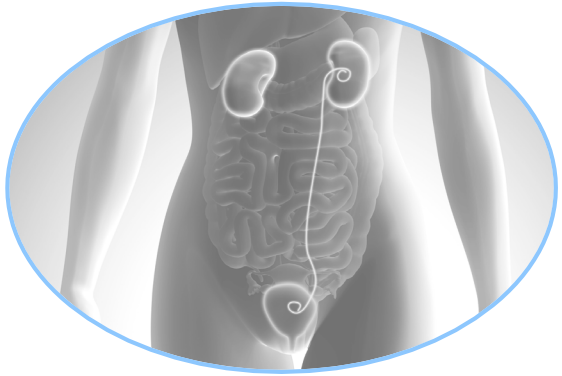

This study was developed by

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