

## A NEW EXPERIMENTAL MODEL FOR INDUCING INTERSTITIAL CYSTITIS BY OXIDATIVE STRESS USING BLADDER INSTILLATION OF A NITRIC OXIDE DONOR GEL

### Hypothesis / aims of study

Interstitial cystitis (IC) is a chronic condition characterized by supra-pubic pain, urgency, frequency and noctúria. The etiology of the IC is still unknown and there are many theories that try to explain it. One of the causes may be an epithelium dysfunction, caused by a defect in the glycosaminoglycans protective layer (GAG) of the vesical wall, which allows the urine to pass to the interstitium leading to an inflammatory process. Patients with IC are usually associated with chronic immunological disorders. These patients would have antibodies against the mucosa cells or the muscular cells, or many other tissues that compose the bladder (3). The regulation of the activity of the nitric oxide synthase (NOS) in the urine is thought to be an important factor in the immunological response in IC. There are findings that lead to increasing as well as decreasing of the levels of NO (NO) in patients with IC, there is no agreement concerning the levels of NO in the bladder of the IC patients. There are no studies on the effects of the NO on the urothelium and the lamina propria of the bladder. The aim of this project is to study the effects of a gel with NO donor on the urothelium and the muscular layer of the bladder of rats comparing to the gold standard cystitis induction method with protamine and potassium chloride.

### Study design, materials and methods

This project is under development at our institution, after approval by the Research Ethics Committee, protocol nº 1296-1. The rats were accommodated in cages containing five animals each, under ideal feeding, temperature, humidity and light conditions. A pilot study including 20 rats was made as a training process for bladder catheterization in the animals.

### Procedure

The animals were divided in four groups:

Group	Treatment
1	Saline + GSNO
2	Saline+ Polymeric Solution
3	Protamine sulfate
4	Protamine + GSNO

1º) Ten rats underwent two sessions of bladder instillation with a 24 hours interval between them of saline solution 0,9% at 0,04 ml/min until bladder overflow is achieved and then they were injected with GSNO solution in 3 doses, 2 days between each dose and after that they were sacrificed.

2º) Ten wistar rats underwent two sessions of bladder catheterization with a 24 hours interval between them of saline solution 0,9% at 0,04 ml/min until bladder overflow. Half of the group were sacrificed after 48 hours and half 7 days after the first infusion

3º) Ten rats underwent two sessions of bladder catheterization with a 24 hours interval between them using protamine solution (30 mg/ml) and KCl 300mM 0,04 ml/min until bladder overflow (when the maximum vesical capacity is obtained) and ingested water; half the group for 48 hours after the first infusion, when they were sacrificed, and the other half 7 days after the first infusion, when they were also sacrificed.

4º) Ten rats underwent two sessions of bladder catheterization with a 24 hours interval between them using protamine solution (30 mg/ml) and KCl 300mM 0,04 ml/min until bladder overflow (when the maximum vesical capacity is obtained) and then they were injected with GSNO solution in 3 doses, 2 days between each dose and after that they were sacrificed

### Results

A similarity was found between the groups Saline + NO and protamine ( $p=0,0035$ ) when it comes to vascular congestion. There was also a significant similarity between the same groups in the fibrosis ( $p=0,0459$ ).

### Interpretation of results

The probable relation between nitric oxide and the IC inflammatory process leads to an attempt of producing an experimental model that is closer to reality and more reliable, with a NO donor gel to start up the inflammatory process.

The findings in the histology of the bladders of the rats, indicating inflammation, show that it is possible to continue these tests so that the IC studies can be developed even further.

### Concluding message

When observing the results of this study, it is possible to affirm that the inflammatory process caused by the intravesical instillation of NO is similar to the experimental model in the literature, and that this procedure can be considered as a new experimental model for inducing interstitial cystitis, for future researches and new treatments.

### References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. : Am J Obstet Gynecol. 2002 Jul;187(1):116-26E. Kelada, A. Jones. Interstitial cystitis. Arch Gynecol Obstet (2007) 275:223-229
2. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. Urology (1997) 48: 2-9
3. Kelada E, Jones A. Interstitial cystitis. Arch Gynecol Obstet. (2007) 275:223-229

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<b><i>Is this a clinical trial?</i></b>	<b>No</b>
<b><i>What were the subjects in the study?</i></b>	<b>ANIMAL</b>
<b><i>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</i></b>	<b>Yes</b>
<b><i>Name of ethics committee</i></b>	<b>Comitê de Ética em Experimentação Animal (Ethics Committee for Animal Experimentation)</b>