

**TOPICAL EFFECTS OF INTRAVESICAL CAPSAICIN ON RAT BLADDER**

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**ABSTRACT**

**Background:** To determine the topical effect of intravesical capsaicin on bladder mucosa in graded doses.

**Methods:** Intravesical reagent was instilled in four groups of age and weight matched female rats: 2, 4 and 40 mM capsaicin and saline. Intravesical capsaicin was dissolved in 30% ethanol (EtOH) and saline. The animals (n = 4 each group) were sacrificed at the 13th day after a total of 5 instillations at days 0, 2, 5, 7 and 10. Whole bladders were harvested, fixed in 10% buffered formalin, and paraffin embedded. Tissue blocks were blind coded and sectioned (5-mm thickness) for histopathological analysis. All sections were stained with hematoxylin and eosin and examined under light microscopy. Fishers' exact test was used for statistical analyze.

**Results:** The rats in intravesical capsaicin groups (2, 4, and 40 mM) exhibited similar bladder mucosal histology. Instillation of saline demonstrated no effect on bladder histology, whereas instillation of intravesical capsaicin induced acute thinning effect of the epithelium, submucosal edema, vascular ectasia and congestion and also eosinophil infiltration, that was statistically insignificant, in some parts of the stroma of only one bladder (25%) in the 40 mM group.

**Conclusions:** All bladders in intravesical capsaicin groups demonstrated a histologically similar mucosa, except for the eosinophil infiltration in some parts of the stroma of a bladder in 40 mM group and which was statistically insignificant. Thus, we conclude that, in the resistant cases treated with intravesical capsaicin, concentrations may be risen up above the widely used doses, if an adequate anesthesia is maintained.

**Key words:** bladder; urinary bladder; rat; cystitis; capsaicin

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**INTRODUCTION**

Red hot chili was introduced in human diet in Mexico 7000 years ago. Capsaicin is a pungent substance which is a derivative of homovanillic acid and is chemically represented by 8-methyl-N-vannilyl-6-nonenamide found in red hot chili peppers (1). A solution of pure capsaicin powder can be made by dissolving it in alcohol and saline. For about the last decade, intravesical capsaicin has been taken into account in urology clinics as a treatment option in detrusor hyperreflexia, hypersensitive disorders of the

lower urinary tract and severe bladder pain (2). In animal models, capsaicin has a neurotoxic effect on unmyelinated C fibers by binding vanilloid receptors located in the bladder mucosa (3). Through the study of the spinal of cats, it has observed that capsaicin blocks the micturation reflex initiated by the C fibers, which are also responsible for the transmission of pain to the spinal cord reducing hyperreflexia (4). A 1 - 2 mmol/l (0.3 - 0.6 g/l) capsaicin solution is widely accepted for intravesical treatment of detrusor hyperreflexia and it should be considered that the concentrations used for hypersensitive bladder are

about 100 times lower than those used for hyperreflexia (5). Recently, it has been reported that capsaicin is no better than placebo for relieving bladder pain, and it was suggested that higher concentrations of capsaicin for painful bladder might be more effective, if adequate anesthesia is maintained during the procedure (6). Pain, during and sometimes after the instillations, is still a common problem in the intravesical use of this drug. Topical capsaicin in a concentration range of 0.01 to 30.0 mM has been used to treat many painful conditions, including postherpetic neuralgia and painful diabetic neuropathy (7,8). In this study, we studied the topical effects of intravesical capsaicin in graded doses on rat bladder mucosa.

## MATERIALS AND METHODS

**Animal model:** Intravesical reagents were instilled in four groups (four animals in each group) of Wistar female rats. Intravesical agents were studied as: 1)- control (intravesical saline only); 2)- normal dose, 2 mmol/l (0.6 g/l) of capsaicin; 3)- high dose, 4 mmol/l (1.2 g/l) of capsaicin; 4)- very high dose, 40 mmol/l (12 g/l) of capsaicin. Rats were matched for age and weight (230-260 grams). Ketamin HCL anesthesia was used during intravesical instillation and bladder harvesting.

**Intravesical instillation:** Ruling out urinary tract infection through urinalysis was performed. Solutions of capsaicin were prepared in 30% ethanol (EtOH). The bladder was catheterized through the urethra and emptied. The intravesical instillation consisted of 1 ml solution of each reagent into the bladder via urethral catheterization. Some leakage was observed. The bladder was emptied 30 minutes after the reagent instillation. Each group contained 4 animals, which were all sacrificed at the 13th day after a total of 5 instillations at the days 0, 2, 5, 7 and 10. Whole bladders were harvested, fixed in 10% buffered formalin and embedded in paraffin.

**Histopathological analysis:** Tissue blocks were blind coded and sectioned in 5- $\mu$ m-thick cuts for histological staining with hematoxylin and eosin (HE). Samples were examined under light microscopy at magnifications of X100 and X200.

Statistical analysis was performed with Fisher exact test.

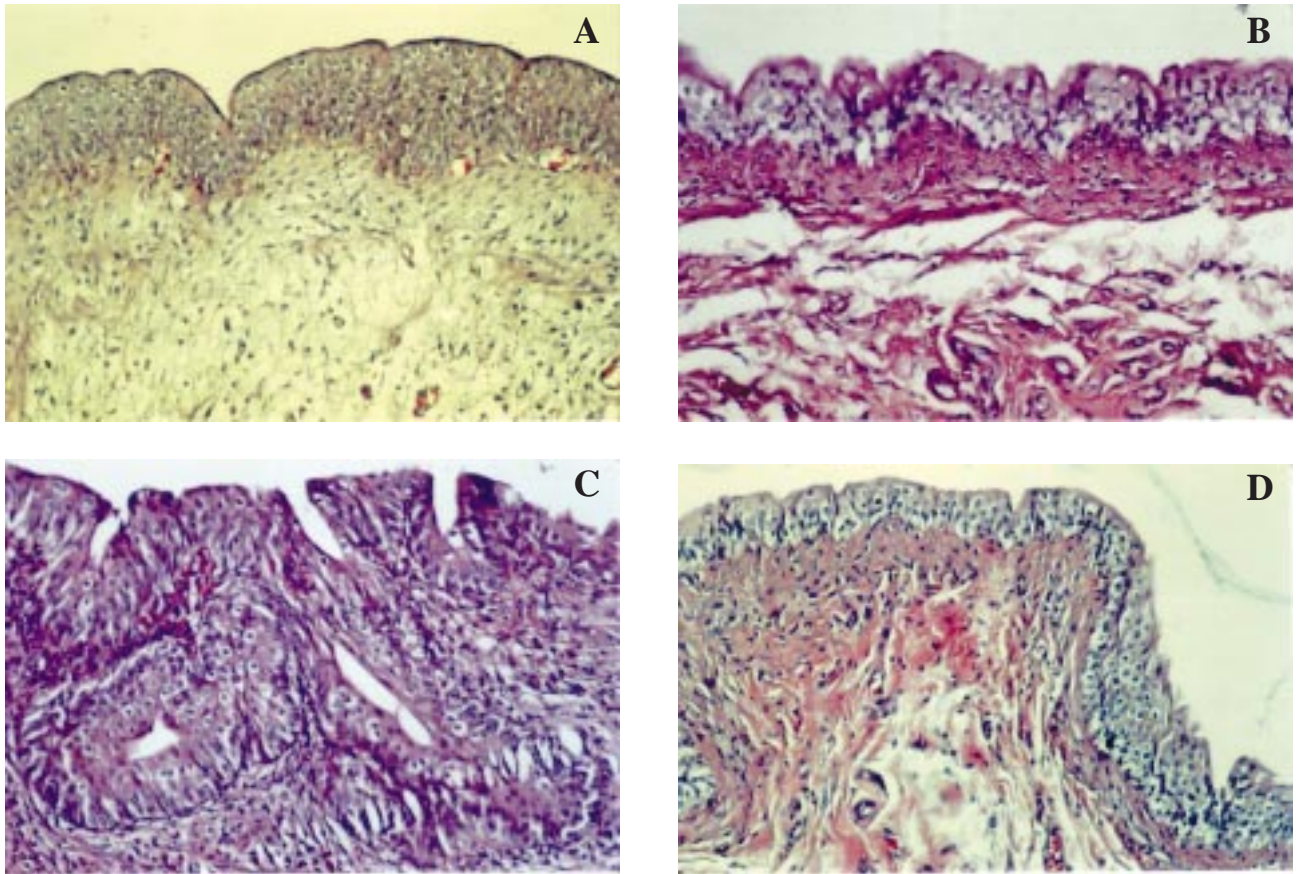
## RESULTS

During the study all animals survived. No systemic signs of toxicity, loss of weight and fur was observed. Urinalysis was performed in all animals post-intravesical instillation and no animals developed a urinary tract infection. Instillation of capsaicin in either doses had the same effect on the bladder mucosa, similar to chemical cystitis, such as acute mucosal injury, submucosal edema, vascular ectasia, vascular congestion and thinning of the epithelium, but not mucosal ulceration (Parts A, B and C of Figure-1). Eosinophil infiltration was noticed in some parts of the stroma in one bladder (25%) in the very high dose group (Figure-2). This was statistically insignificant ( $p = 1$ ). The bladders in control group did not show any pathology (Part D of Figure-1).

## DISCUSSION

It is well known that capsaicin has been a constituent of human diet for thousands of years without any long-term side effects (9). In painful conditions such as postherpetic neuralgia and painful diabetic neuropathy, topical capsaicin has been used in a range of concentrations between 0.01 to 30.0 mM. (7,8). Neither systemic absorption of capsaicin after single or repeated administration nor evidence of permanent damage to nerves or tissues in the treated area was observed (10). Burning sensation at the site of application is the most reported complaint (11). Most patients with intractable detrusor hyperreflexia would be treated with indwelling catheters and those disabled would be submitted to operative procedures to achieve continence. Therefore, intravesical capsaicin as an effective therapy for detrusor hyperreflexia became popular in urological practice.

In animal experiments, it was shown that response to intravesical capsaicin depends on the concentrations (12). Tolerable intravenous capsaicin for adults is about 0.3 mg in the literature (13). So it is widely accepted, but not consistent, that the maximum intravesical concentrations of capsaicin is

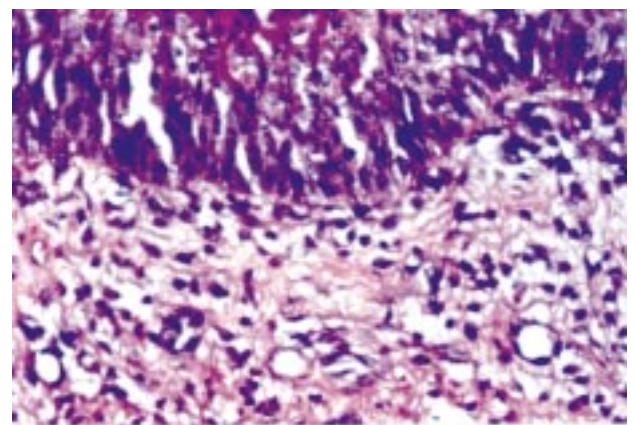


**Figure 1 -** A)- to C)- Bladder histology of rats in intravesical capsaicin groups, submitted to graded doses of 2, 4 and 40 mM, respectively. The alterations include acute mucosal injury, thinning of the epithelium, submucosal edema, vascular ectasia, and congestion; D)- Control group after instillation of saline demonstrated no effect on the bladder mucosa. (HE, A and D, X100; C and D, X200).

2 mmol/l because of the systemic absorptions of the agent by the bladder wall (5). In our study, even though we reach to the intravesical dose of 40 mmol/l, we did not observe any systemic complication. Local side effects of capsaicin as suprapubic or urethral pain, burning sensation, gross hematuria, urgency appears during and for several days after the instillation, and resolve within either 1 - 3 days in nonneurologic patients or 15 days in neurologic ones (2). Tachyphylaxis to the burning lasted mostly not more than 72 hours, but may go on to a time of 4 weeks (11).

While general anesthesia seems to be not helpful because the agents used would not relax the detrusor in spinal cord injury patients (14) and epidural anesthesia needs specialist assistance, use of local anesthesia appears to be the best option because of its better general tolerance without affecting the efficacy

of capsaicin (15). Although the instillation of lidocain 2% before capsaicin made the procedure easier, it did



**Figure 2 -** Eosinophil infiltration in the stroma of one bladder of the very high dose capsaicin instillation group. (HE, X200).

not provide adequate local anesthesia in all patients. Electromotive drug administration (EMDA) of lidocaine in local anesthesia was offered for these patients as simple office technique, that does not require specialized training (5).

In animal models, capsaicin and chillies have been claimed possible carcinogens (16-19) and also, in a case control epidemiological study, where confounding factors were not controlled, they suggested a 17-fold increase in the risk of gastric cancer in people consuming large amounts of chili in their diet (20). On the other hand, inhibitory effect of capsaicin on mouse lung tumor development has also been reported (1). It was shown that not only is intravesical capsaicin a safe treatment over a period of 5 years follow-up but also the inflammation caused by capsaicin obviously settles down within a few weeks of treatment and the urothelium reverts back to its original appearance (1). As similar, minor and moderate degree of recovery was noted at 24 and 72 hours respectively after 1 mM standard intravesical capsaicin, and at the end of one week the histological appearance of the bladder mucosa was similar to the non-treated bladder mucosa (11). Though our groups were arranged with the graded doses of 2, 4, and 40 mM, we did not observe any serious systemic complication or unusual topical effect in the bladder mucosa, except for moderate inflammation. Eosinophil infiltration was seen in some parts of the stroma of the bladder in only 1 animal (25%) in 40 mM group, and this may be a result of an allergic reaction against the drug, even though statistically insignificant.

Our study suggests that in the resistant cases treated with intravesical capsaicin, concentrations may be risen up above the widely used doses if an adequate anesthesia is maintained.

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