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POROUS BIOCERAMIC PARTICLES, A NEW BULKING AGENT FOR TREATMENT OF STRESS URINARY INCONTINENCE.

<u>Hypothesis / aims of study</u>

An ideal urethral bulking agent for treatment of stress urinary incontinence should be biocompatible and easy to inject, provide volume retention and it should not migrate.[1] New biocompatible alumina-based ceramic particles were recently developed using material similar to that in hip prostheses.[2] These microspheres are porous and tissue in growth into the pores has been documented, suggesting that if this material is to be used as a bulking agent to treat stress urinary incontinence, urethral tissue in growth could prevent its migration. The goal of this study is to provide morphological evaluation of the rat urethra and functional evaluation of the lower urinary tract following intraurethral injection of the microporous ceramic spheres (100 microns diameter).

<u>Study design, materials and methods</u>

Bioceramic particles have been injected into the proximal urethra of 8 female rats. Under general anesthesia a lower midline abdominal incision was performed and the proximal urethra was identified. Bioceramic particles suspended in PVP 40 gel have been injected using 18 gauge needle into both lateral walls of the proximal urethra using 2 injections. An outcome of the injection has been photographed intraoperatively using a camera attached to the operating microscope (40x magnification). An additional 8 rats were injected with saline only. Before the surgery and six to eight weeks following injection the function of the lower urinary tract was evaluated by placing the animal separately into a metabolic cage and recording frequency of micturition, voided volume and mean urinary flow rate. Subsequently animals were euthanized, proximal urethral was isolated with the position of the beads has been photographed again. Volume retention has been estimated by comparing the microphotographs immediately after injection to those taken 6 to 8 weeks following injection. Urethral tissue has been harvested and evaluated histologicaly. Study was performed in accordance with institutional and national animal care and use guidelines.

<u>Results</u>

The bioceramic spheres were successfully injected into the proximal urethra in all 8 animals. The injection has been repeated due to needle obstruction in four of the total number of 16 injections. All the injections were performed successfully resulting in symmetric bulking effects on both sides of the urethra (3 and 9-o-clock position). No statistical difference in the number of micturitions, average voided volume or mean urinary flow rate has been observed prior to injection or 6 – 8 weeks after. (Table)

	Intermicturition Interval (min)	**Voided Volume (mL)**	**Mean Flow Rate (mL/s)**
Pre-injection	32.3 ± 5.35	0.55 ± 0.16	0.16 ± 0.02
Post-injection	32.3 ± 0.79	0.45 ± 0.05	0.13 ± 0.02

Table: Summary of the data from behavioural study. Rats were placed into metabolic cage with free access to food and water. The bottom of the cage is made of a grid that allows urine to freely fall onto a collecting device placed on top of the analytical balance. This allowed for recording of voiding frequency, voided volume and mean urinary flow rate.

Comparison of microphotographs before injection and 6 – 8 weeks after showed good volume retention. (Figure) No beads were found on serial cross-sections of liver, kidneys and lungs in the randomly selected 4 animals. On cross-section the majority of the bulking agent has been retained in the submucosa. No signs of inflammation or fibrosis were documented on the histological evaluation. We were unable to evaluate the tissue growth into the pores of the beads due to the opaque nature of the beads and lack of access to scanning electron microscopy.

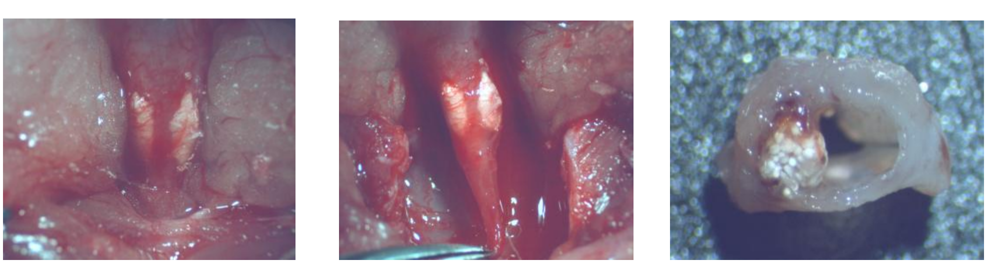

Figure: Microphotograph showing bulking agent immediately after injection into the wall of the proximal urethra (left) and 6 weeks following the injection (middle). The cross section (right) shows majority of the ceramic beads located in the sumucosa.

<u>Interpretation of results</u>

The microporous bioceramic particles could be injected into the urethral wall. The biocompatibility evident from the use of this material in orthopedics has been confirmed in an urologic setting by our study. Our preliminary studies showed good volume retention with no signs of migration. More studies are necessary to address the issues of host tissue in growth into particles and possible embolization of particles into distant organs. Our functional studies suggest that injections do not result in bladder outflow obstruction.

Concluding message

This pilot study performed on a murine model suggests that alumina coated porous bioceramic particles could be developed into an urethral bulking agent for the treatment of stress incontinence.

References

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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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