Published in final edited form as:

J Urol. 2012 May ; 187(5): 1898–1902. doi:10.1016/j.juro.2011.12.057.

Comparison of Intraprostatic Ethanol Diffusion Using a Microporous Hollow Fiber Catheter Versus a Standard Needle

Benjamin J. King, Mark K. Plante^{*}, Masatoshi Kida, Travis K. Mann-Gow, Rick Odland[†], and Peter Zvara[‡]

Department of Surgery, Division of Urology (BJK, MKP, TKMG, PZ), and Department of Pathology (MK), University of Vermont, Burlington, Vermont, and Departments of Otolaryngology, Hennepin County Medical Center and University of Minnesota, and Twin Star Medical, Inc., Minneapolis (RO), Minnesota

Abstract

Purpose—Transurethral intraprostatic ethanol chemoablation of the prostate has shown promising preliminary clinical results for benign prostatic hyperplasia with some variability in clinical outcome. This is likely due to the uneven prostate diffusion caused by varying resistance of the tissue type in which the tip of the needle is embedded. We examined whether the distribution of the injectable in the canine prostate could be improved using a microporous hollow fiber catheter (Twin Star Medical, Minneapolis, Minnesota).

Materials and Methods—The prostate was exposed in 9 mongrel dogs. A single injection of 98% ethanol was delivered in each lobe using a microporous hollow fiber catheter and a standard needle. Prostates were harvested and fixed in 10% formalin. After injection 2.5 mm step sections were obtained and scanned. The ethanol induced tissue lesions were traced on hematoxylin and eosin sections. Three-dimensional reconstructions were created and the volume of each prostate lesion was calculated using stereology.

Results—Ethanol induced tissue changes were seen bilaterally in 8 of 9 ethanol injected prostates. In all cases the lesion created by microporous hollow fiber catheter injection was larger than that in the contralateral lobe injected with the control needle. When data were pooled, the hollow fiber catheter injection produced significantly greater tissue changes than the control needle injection ($p = 0.03$).

Conclusions—Improved distribution and absent backflow were seen when using the microporous hollow fiber catheter, supporting its potential as a new method to treat prostate disease.

Keywords

prostate; injections; catheters; needles; instrumentation

The last decades have seen continued interest in new minimally invasive treatments for prostate disease. However, more development is needed to improve treatment efficacy and reproducibility.¹

© 2012 by American Urological Association Education and Research, Inc.

[‡]Correspondence: Division of Urology, Department of Surgery, University of Vermont, D319 Given Building, 89 Beaumont Ave., Burlington, Vermont 05405 (telephone: 802-656-3465; FAX: 802-656-0680; peter.zvara@uvm.edu).

^{*}Financial interest and/or other relationship with Omni Medical.

[†]Financial interest and/or other relationship with Twin Star Medical.

Study received University of Vermont institutional animal care and use committee approval.

Prostate ablation by direct injection has the potential to significantly decrease morbidity while providing a simple procedure that improves outcomes. We previously reported that the prostate capsule acts as a barrier that prevents the injected substance from diffusing beyond the organ, making it a suitable target for drug delivery using direct intraprostatic injection.^{2,3}

The potential advantage of injection compared to other minimally invasive treatments, such as radio frequency energy and microwaves, is the ability to effectively ablate tissue.⁴ Prostate ablation using intraprostatic ethanol injection has been studied in canine experiments and clinical trials. It showed promising results but variability was documented in the tissue distribution pattern. Variable clinical outcomes were also reported,^{5–8} likely due to varying resistance of the tissue type in which the needle tip was embedded (stroma, muscle or glandular tissue) as well as backflow of the substance along the needle tract.³

CED could be a possible solution to the asymmetrical distribution and backflow of prostate injection. CED uses flow or convection through the interstitial space with slow infusion. CED was first described for brain infusion using small needles^{9–11} but further improvement has been achieved with an MiHFC instead of a needle.

An MiHFC consists of small tubules with millions of nanoscale pores throughout the walls of the hollow fiber. This greatly increases the surface area of infusion, resulting in lower flow velocity and better interstitial distribution at an equivalent drug delivery rate, allowing the injected substance to diffuse through an area significantly larger than that of a standard single lumen needle. Compared to a standard needle, a hollow fiber catheter showed improved distribution in studies using tissue phantoms and animal brain.^{12,13}

We compared the efficacy and diffusion pattern of the MiHFC CED to those of a standard single lumen needle in vivo in a canine prostate as a potential method of improving tissue diffusion and backflow elimination.

MATERIALS AND METHODS

This protocol was approved by the University of Vermont institutional animal care and use committee. All animals were treated humanely in accordance with National Institutes of Health policies.

Experiment

Nine mongrel dogs 6 months to 2 years old were used for intraprostatic injection of 0.05% methylene blue diluted in AE solution. The experiment was done with the dogs under general endotracheal anesthesia using 2.5% isoflurane.

With the dog in the dorsal lithotomy position a 5Fr compliant urethral balloon catheter (TechDevice, Water-town, Massachusetts) was inserted. The balloon was inflated with 2 ml distilled water in the membranous urethra distal to the prostate to serve as a plug preventing leakage of injected solution distal into the urethra.

A lower midline abdominal incision was made to expose the bladder. A stay suture was placed in the bladder dome. The prostate was exposed by pulling the suture cranial and bluntly dissecting surrounding tissue. After prostate measurement the volume was determined using the ellipsoid formula, $0.524 \times \text{craniocaudal} \times \text{transverse} \times \text{dorsoventral}$ dimension.

Based on our previous studies the volume of AEMB solution used was equivalent to 25% of total prostate volume. This volume was divided into 2 equal injections with each lobe receiving 12.5% of the total prostate volume.

A single injection of AEMB solution was performed in each lobe. The single lumen 21 gauge control needle with an inner and outer diameter of 514 and 819 μm , respectively, was used to inject 1 lateral prostate lobe. The MiHFC with an inner and outer diameter of 280 and 360 μm , respectively, was used to inject the contralateral lobe. The needle was deployed at the base of the prostate, aiming toward the apex with a trajectory such as that planned in human trials for transrectal ultrasound guided needle insertion (fig. 1, A). Three lengths of MiHFC (1, 1.5 and 2 cm) were used based on prostate size.

The tip of the single lumen control needle was inserted into the geometrical center of the prostate lobe. the MiHFC was placed using an especially designed catheter deployment system (Twin Star Medical). The catheter tip was greater than 3 mm from the capsule and the distal end of the fiber was greater than 6 mm from the capsule (fig. 1, B). The prostate of dog 10 was harvested without injection to serve as a histological control.

The infusion rate was controlled using a Legato 210 Infuse/Withdraw Syringe infusion pump (KD Scientific, Holliston, Massachusetts). The flow rate for each trial was based on the length of the MiHFC used (250 μl per minute per cm of membrane). The same flow rate was used to inject the contralateral lobe with the control needle. Injection pressure was monitored during each trial and the needles were withdrawn after allowing pressure to decrease and level off. Allowing pressure to return to baseline ensured that equal volumes were delivered, although infusion pressure varied while the pump was on.

At the conclusion of each injection the urethra was flushed with 5 ml distilled water through the urethral catheter. The fluid (distilled water, urine and leaked solution) was collected from the bladder. The total volume of liquid was recorded and samples were analyzed to determine the ethanol level. The total volume and ethanol concentration in collected fluid was used to calculate the total volume of leaked solution using the equation, ethanol concentration in leaked solution $\times$ volume of collected fluid.

Immediately after flushing the bladder the prostate was harvested and fixed en bloc in 10% neutral buffered formalin. The surgical portion of this experiment was completed by necropsy. Adjacent bladder and rectum tissues were evaluated macroscopically to look for any evidence of methylene blue dye leakage along the needle tract outside the prostate.

Tissue Processing and Histopathology

After 24-hour fixation with 10% neutral buffered aqueous solution of formaldehyde (neutral buffered formalin) the prostates were sectioned perpendicular to the urethral axis into 2.5 mm step sections. A glass slide with 5 μm prostate tissue was made from each step-sectioned prostate for hematoxylin and eosin staining.

An MZ6 stereomicroscope fitted with a DFC280 camera (Leica Microsystems, Heerbrugg, Switzerland) was used to convert histology slides into digital images. Images were analyzed by a blinded pathologist (MK) and lesions were traced in Photoshop® CS4. The lesion area was defined as severe—complete cellular ablation and/or complete loss of normal acinar architecture by cellular fragmentation or marked dilatation of acinar and ductal lumens, or moderate—incomplete cellular ablation with preservation of normal acinar architecture. Areas with lesional changes were delineated from the neighboring nonlesional prostate tissue with a line marker on screen.

Lesion Volume Assessment

Using the unbiased stereology software Stereo Investigator 9.14.5 (Microbrightfield Bioscience, Williston, Vermont) we calculated the area and volume of the entire prostate, and of individual lesions using the Cavalieri estimator probe. The mounted thickness of the

slides converted into digital images was 5 μm and the sectional interval was 2.5 mm. Using the digital images in Stereo Investigator the contours and lesions were traced and stacked images were reconstructed for volumetric analysis (fig. 2, D). Sections were stacked by visually aligning the outlines of adjacent sections. The urethra served as a central point to ensure proper alignment among serial sections. We used 8 to 14 sections per prostate to analyze and create 3-dimensional images of the lesions. Calculated and estimated lesion volume, and maximal infusion pressure were compared using the paired t test.

RESULTS

Infusion pressure seen with the control needle was typically higher than that with the MiHFC (fig. 3). Average $\pm$ SD infusion pressure for all studies was 409.6 ± 134 and 352.6 ± 182.0 mm Hg for the control needle and the MiHFC, respectively.

No backflow was observed along the needle tract during any injection with the MiHFC or the control needle. Six injections were associated with leakage of AEMB solution into the prostatic urethra. This was recorded 4 times for the control needle and twice for the MiHFC. For the 4 instances of leakage for the control needle and the 2 for the MiHFC average volume was 4.9% (7.72%, 9.3%, 8.71% and 0.44%) and 6.5% (2.66% and 7.19%, respectively) of total injected volume.

Macroscopically the prostate of the control dog appeared tan, smooth and homogenous. No pathological abnormalities were noted. Gross evaluation of the 9 experimental prostates revealed areas of methylene blue diffusion into the injected lobes using the control needle and the MiHFC (fig. 2, A). There was clear variability in intraprostatic distribution seen for each delivery system.

Under microscopy lesion volume was compared to the volume of the entire lobe. In a single prostate no lesion was observed on either side. The remaining 8 prostates showed tissue lesions bilaterally. In all 8 cases the lesion created with the MiHFC injection was larger than that in the contralateral lobe injected with the control needle (fig. 4). When data were pooled, the average size of the lesion created by the MiHFC was $0.82 \pm 0.31 \text{ cm}^3$ while that of the control needle was $0.52 \pm 0.21 \text{ cm}^3$. The difference between the 2 average values was significant ($p = 0.03$).

Three-dimensional reconstruction of the lesions revealed variations in shape ranging from round to oblong. In most instances the craniocaudal limits of the lesions demonstrated sharp demarcations (fig. 5, A and B). In some prostates injection with the control needle created lesions limited to only a thin narrow area along the needle tract, in contrast to those created with the MiHFC (fig. 5, C).

DISCUSSION

Continued interest in finding more effective minimally invasive alternative therapies for prostate pathology along with new therapeutic agents supports the ongoing evolution of intraprostatic injection as a potentially viable treatment for various prostate diseases.¹ The anatomical site of the prostate and refined imaging techniques make the prostate easily accessible via a transrectal route.

Our preclinical canine studies demonstrated that intraprostatic AE injection creates coagulative necrosis surrounded by acute and chronic inflammation with focal areas of hemorrhage and edema.¹⁴ Use of a single lumen needle was associated with varying degrees of injection resistance and significant backflow along the needle track.³ Our preclinical chronic study in 22 dogs confirmed that transurethral intraprostatic ethanol injections

diffused irregularly with unpredictable resultant lesion size.⁵ In that study the extent of tissue necrosis after injection was 0% to 95% of prostate lobe volume.

Variability in clinical outcome was also noted in subsequent multicenter clinical trials of transurethral ethanol ablation of the prostate.^{6–8} Since the conclusion of these studies, new potential injectables suitable for intraprostatic injection have been introduced.^{15–18}

By its nature transrectal intraprostatic injection compromises prostate capsule integrity. Potential backflow along the needle tract could result in injectable leakage into the periprostatic area. Thus, transrectal intraprostatic injection necessitates solid preclinical evidence showing the lack of back-flow. This was documented in our study.

Transrectal ultrasound guided intraprostatic injection is impossible in a dog due to prostate mobility. Our alternative method using direct injection into the exposed prostate allowed us to circumvent this limitation. The infusion rate of 250 μ l per minute per cm, which was determined in prior ex vivo experiments, was the fastest flow rate that could be used without backflow.

Infusion pressure varied and lower pressure was associated with a larger diffusion area. The lower mean pressure noted for the MiHFC was expected, given that it has a substantively larger surface area than a standard needle. The estimated area of the approximately elliptical opening of a beveled 21 gauge needle is 40 to 80 times smaller than the surface area of the 1 to 2 cm hollow fibers. Thus, outflow velocity is 40 to 80 times slower for the hollow fiber than for needle infusion at the same flow rate. Interstitial uptake of the infused drug can occur at a slower rate, making it less likely that infusion velocity will exceed the interstitial flow velocity of the tissue. As a result, the MiHFC showed more uniform delivery.

In contrast to our previous study, we did not observe backflow along the needle tract during injections using the standard needle or the MiHFC. This may have been due to the slow, steady infusion rate controlled by the syringe pump, in contrast to the manual injection used in previous studies.

Methylene blue allowed us to evaluate the presence or absence of injected solution outside the prostate. AE injection led to histological changes in exposed tissue. We used hematoxylin and eosin staining to identify histological changes and quantify the volume of affected tissue. Three-dimensional reconstruction showed lesions of varying sizes and shapes. Each dog served as its own control since prostates were injected with an MiHFC or a control needle in the right and left prostate lobe, respectively.

Overall lesions of variable sizes were created. In all cases the lesion was larger on the side of MiHFC injection. On 3-dimensional reconstruction most lesions were oval with sides that ended abruptly in a flat plane. The distance of 2.5 mm between sections could account for this phenomenon. However, as evident on individual sections and gross specimens, this could have been due to a barrier function of the intraprostatic septa in the canine prostate. The canine prostate is composed of approximately 17% acini and ducts while the remaining 63% is solid glandular tissue.¹⁹ To some degree this limits its applicability as a surrogate of human prostates. The long, narrow lesions seen using the control needle suggest backflow (fig. 5, C), given proximal tracking of the AEMB solution.

CONCLUSIONS

Injection with an MiHFC in a canine prostate resulted in improved distribution of injected solution compared to that using a standard needle. Using an infusion pump backflow was

not seen for either injection method. Together these findings support further investigation of the MiHFC in clinical trials.

Acknowledgments

Supported by National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases R43 DK085810.

Abbreviations and Acronyms

AE	98% anhydrous ethanol
AEMB	anhydrous ethanol and methylene blue
CED	convection enhanced delivery
MiHFC	microporous hollow fiber catheter

References

1. Donnell RF. Minimally invasive therapy of lower urinary tract symptoms. *Urol Clin North Am*. 2009; 36:497. [PubMed: 19942048]
2. Zvara P, Karpman E, Stoppacher R, et al. Ablation of canine prostate using transurethral intraprostatic absolute ethanol injection. *Urology*. 1999; 54:411. [PubMed: 10475344]
3. Plante MK, Gross AL, Folsom JB, et al. Diffusion properties of transurethral intraprostatic injection. *BJU Int*. 2004; 94:1384. [PubMed: 15610125]
4. Plante MK, Marks LS, Anderson R, et al. Phase I/II examination of transurethral ethanol ablation of the prostate for the treatment of symptomatic benign prostatic hyperplasia. *J Urol*. 2007; 177:1030. [PubMed: 17296405]
5. Plante MK, Gross AL, Kliment J, et al. Intraprostatic ethanol chemoablation via transurethral and transperineal injection. *BJU Int*. 2003; 91:94. [PubMed: 12614259]
6. Grise P, Plante M, Palmer J, et al. Evaluation of the transurethral ethanol ablation of the prostate (TEAP) for symptomatic benign prostatic hyperplasia (BPH): a European multi-center evaluation. *Eur Urol*. 2004; 46:496. [PubMed: 15363567]
7. Buchholz NN, Andrews HO, Plante MK. Transurethral ethanol ablation of prostate. *J Endourol*. 2004; 18:519. [PubMed: 15333212]
8. Mark K, Plante JP, Martinez-Sagarra Jose, et al. Complications associated with transurethral ethanol ablation of the prostate for the treatment of benign prostatic hyperplasia: a worldwide experience. *J Urol*. 2003; 169:392.
9. Lieberman DM, Laske DW, Morrison PF, et al. Convection-enhanced distribution of large molecules in gray matter during interstitial drug infusion. *J Neurosurg*. 1995; 82:1021. [PubMed: 7539062]
10. Bobo RH, Laske DW, Akbasak A, et al. Convection-enhanced delivery of macromolecules in the brain. *Proc Natl Acad Sci USA*. 1994; 91:2076. [PubMed: 8134351]
11. Laske DW, Morrison PF, Lieberman DM, et al. Chronic interstitial infusion of protein to primate brain: determination of drug distribution and clearance with single-photon emission computerized tomography imaging. *J Neurosurg*. 1997; 87:586. [PubMed: 9322847]
12. Oh S, Odland R, Wilson SR, et al. Improved distribution of small molecules and viral vectors in the murine brain using a hollow fiber catheter. *J Neurosurg*. 2007; 107:568. [PubMed: 17886557]
13. Oh S, Tsai AK, Ohlfest JR, et al. Evaluation of a bispecific biological drug designed to simultaneously target glioblastoma and its neovasculature in the brain. *J Neurosurg*. 2011; 114:1662. [PubMed: 21294620]
14. Littrup PJ, Lee F, Borlaza GS, et al. Percutaneous ablation of canine prostate using transrectal ultrasound guidance. Absolute ethanol and Nd:YAG laser. *Invest Radiol*. 1988; 23:734. [PubMed: 3056869]

15. Nikoobakht M, Daneshpajoo A, Ahmadi H, et al. Intraprostatic botulinum toxin type A injection for the treatment of benign prostatic hyperplasia: initial experience with Dysport. *Scand J Urol Nephrol.* 2010; 44:151. [PubMed: 20201752]
16. Chapple C. Intraprostatic injection therapy for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Eur Urol.* 2011; 59:755. [PubMed: 21330048]
17. Barton KN, Stricker H, Elshaikh MA, et al. Feasibility of adenovirus-mediated hNIS gene transfer and (131)I radioiodine therapy as a definitive treatment for localized prostate cancer. *Mol Ther.* 2011; 19:1353. [PubMed: 21587209]
18. Chuang YC, Yoshimura N, Wu M, et al. Intraprostatic capsaicin injection as a novel model for nonbacterial prostatitis and effects of botulinum toxin A. *Eur Urol.* 2007; 51:1119. [PubMed: 17141941]
19. Wientjes MG, Zheng JH, Hu L, et al. Intraprostatic chemotherapy: distribution and transport mechanisms. *Clin Cancer Res.* 2005; 11:4204. [PubMed: 15930358]

Figure 1.

A, needle deployment started at anterior prostate base and was directed toward apex. *B*, placement of MiHFC and control needle during intraprostatic injection.

Figure 2.

A, after injection prostate was sliced at 2.5 mm and photographed. *B*, sections were stained with H & E and converted to digital image. *C*, lesion was examined and traced in Photoshop before using Cavalieri estimator probe with software to map and trace lesions and calculate total volume. *D*, 2.5 mm step sections were stacked to enable 3-dimensional reconstruction. Control needle injection site was on right side and MiHFC injection was on left side.

Figure 3.
Intraprostatic pressure/resistance during intraprostatic injection using MiHFC (blue curve) and conventional needle (red curve) in single experiment.

Figure 4. AE lesion size in canine prostate lobes after MiHFC (gray bars) vs control needle (black bars) injection. In experiment 8 no change was noted in either lobe. Each pair of bars represents individual experiment.

Figure 5.

A to C, 3-dimensional reconstructions show lesions created by control needle (blue areas) and by MiHFC (white areas). MiHFC created visibly larger lesion than control needle. C, lesion along control needle length suggests backflow along needle tract.