The Effect of Transarterial Prostate Embolization in Hormone-induced Benign Prostatic Hyperplasia in Dogs: A Pilot Study

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PURPOSE: To evaluate the feasibility of transarterial prostate embolization for reducing the volume in hormone-induced canine prostate hyperplasia.

MATERIALS AND METHODS: Nine beagle dogs were included in this study. Prostate hyperplasia was induced by administering dihydrotestosterone and β-estradiol. The hormones were given for 12 weeks in group A (n = 4) and 24 weeks in group B (n = 5). Twelve weeks after initiating the hormone treatment, two animals in group A and three in group B underwent prostate embolization with polyvinyl alcohol (PVA) particles. The volume of each prostate was measured three times with magnetic resonance (MR) imaging: once before hormone treatment and at 12 and 24 weeks after initiation of hormone administration. The prostates and bladders were harvested after the third MR study and were grossly and microscopically evaluated.

RESULTS: The mean volume of the prostate increased by 156.13% ± 110.01% in the nine dogs after 12 weeks of hormone administration. In group A (n = 4), the third MR study showed a 67.74% mean decrease in prostate volume in nonembolized dogs and an 81.04% mean decrease in embolized dogs compared with the second MR study. In group B (n = 5), the mean increases in prostate volume between the second and third MR studies were 40.79% in embolized dogs (n = 3) and 75.15% in nonembolized dogs. There was no gross or microscopic change in the bladders except for a focal hemorrhage in one specimen.

CONCLUSIONS: Transcatheter arterial embolization is feasible for reducing prostate volume without serious complications in hormone-induced canine prostate hyperplasia.


Abbreviations: BPH = benign prostate hyperplasia, PVA = polyvinyl alcohol

BENIGN prostate hyperplasia (BPH) is the most common human neo-

plasm and is the most common reason for surgical intervention among elderly men (1,2). Although medications such as α-blockers and 5α-reductase inhibitors are widely accepted therapies for treating mild to moderate lower urinary tract symptoms, surgical treatment remains a cornerstone in the treatment of BPH (3,4). Currently, transurethral prostatectomy is accepted as the gold standard for surgical intervention. However, for those patients at high operative risk or those unsuitable for surgery, various minimally invasive treatment modalities have emerged, including laser therapy, cryoablation, and intraprostatic injection of ethanol (5–12). However, the results of these new modalities are not superior to those of transurethral prostatectomy, and they have their own limitations.

Prostate embolization has been performed successfully in patients with bleeding after prostatic biopsy, transurethral prostatectomy, or pelvic urological malignancies (13–16). In addition, there was a case report that transarterial prostate embolization using polyvinyl alcohol (PVA) was effective in reducing the prostate volume and relieving urinary symptoms in a patient with BPH (17). Transarterial PVA embolization of symptomatic BPH is minimally invasive, does not require general anesthesia, and appears to be an effective modality not only in controlling bleeding, but also in relieving voiding difficulties.

Analogous to uterine artery embo-
lization for symptomatic myomas, transcatheter arterial embolization of the prostate may be an alternative treatment for symptomatic BPH (17). Darewicz et al (18) reported an animal experiment on prostatic embolization using histoacryl glue. However, this procedure has not been performed in a BPH model and the change in the size of the prostate and surrounding organs was not reported. According to published reports, BPH can be induced in beagles with hormone administration (19–22) and then prostate embolization with PVA particles can be performed.

The aims of this study were to present our experience inducing an animal BPH model with a combination of hormones and to evaluate the feasibility of transarterial prostate embolization for reducing the volume in hormone-induced canine prostate hyperplasia, before clinical application.

MATERIALS AND METHODS

This protocol was approved by our institutional animal care and use committee. Nine male beagle dogs (age, 11–18 months; weight, 11.5–17 kg) were included.

Induction of Prostate Hyperplasia

The animals were castrated by an urologist. Intramuscular enrofloxacin (5 mg/kg) was injected daily for 3 days to prevent infection. After 4 weeks for involution, 25 mg of dihydrotosterone (5α-androstan-17β-ol-3-one; Sigma-Aldrich, St Louis, Missouri) combined with 0.25 mg of β-estradiol (Sigma-Aldrich) was injected in all beagles three times per week. The hormones were suspended or dissolved in 1 mL of triolein and then injected subcutaneously over the dorsal, posterior cervical region.

In group A (n = 4), the hormones were administered for 12 weeks, and in group B (n = 5), the hormones were injected for 24 weeks.

MR Imaging

The beagles were sedated with an intramuscular injection of sedatives (ketamine 10 mg/kg, xylazine 3.45 mg/kg, and atropine 0.04 mg/kg). The prostate was imaged with use of a quad-knee coil (Invivo, Milwaukee, Wisconsin); axial T2-weighted fast spin-echo and axial T1-weighted spin-echo images with a field of view of 12 or 16 cm and a slice thickness of 5 mm in a 256 × 224 matrix were obtained with use of a 1.5-T magnetic resonance (MR) imaging system (Signa; GE Medical Systems, Milwaukee, Wisconsin).

The volume of each prostate was measured three times in all dogs with MR imaging: before the hormone treatment and 12 and 24 weeks after the initiation of hormone administration (Fig 1). The volume was measured by three radiologists with 2 and 10 years of experience in MR imaging, respectively, and a picture archiving and communication system was used (PiViewSTAR; Infinitt, Seoul, Korea). On the T2-weighted images, the outline of the prostate was drawn and the PACS system calculated the area of the drawn image automatically. The volume of the prostate (in mL) was calculated as the sum of the areas in each image multiplied by the slice thickness.

Embolization

In group A (n = 4), two dogs underwent transcatheter arterial embolization 12 weeks after initiation of hormone injections; embolization was not performed in the other two dogs. In group B (n = 5), three dogs underwent embolization 12 weeks after initiation of hormone treatment; embolization was not performed in the other two dogs.

Anesthesia was administered according to the same method used for the MR imaging studies. An additional half dose of the drugs was injected during the procedure if needed. The right or left inguinal area was prepared for angiography, and a vas-
cular surgeon dissected out the common femoral artery. A 5-F sheath (Radifocus Introducer II; Terumo, Tokyo, Japan) was inserted through the common femoral artery, and pelvic angiography was performed with use of a 5-F angiographic catheter (Tempo; Cordis, Miami, Florida). After angiography of the pelvis and both internal iliac arteries, the arteries supplying the prostate were selected with use of a microcatheter (Renegade; Boston Scientific, Watertown, Massachusetts) and embolization was performed with 250–355-μm PVA particles (Contour; Boston Scientific). Embolization was ended when flow stasis was achieved. The procedure was completed after follow-up angiography and sealing of the cutdown site.

Pathologic Findings

Within 48 hours after the third MR imaging study, the dogs were euthanized with an intravenous injection of pentobarbital followed by 20 mEq of potassium chloride. Then, the prostate and bladders were harvested and evaluated grossly and microscopically by a pathologist.

Statistical Analysis

With regard to the interobserver agreement among the three readers of prostate volume measurement, the Pearson correlation elucidated bivariate relationships between each pair of readers. In groups A and B, differences in prostate volume change were obtained between embolized and non-embolized dogs with the Mann-Whitney U test. Two-tailed P values less than .05 were considered to indicate significant differences. Statistical analysis was performed with SPSS software (version 13; SPSS, Chicago, Illinois).

RESULTS

Angiographic Findings

Angiography of both internal iliac arteries showed contrast agent staining of the prostate, suggestive of BPH. All the supplying arteries were inferior vesical arteries, which were hypertrophied. In all but one dog that underwent embolization, the prostatic arteries branching from the inferior vesical arteries were selected successfully. In one dog (dog no. 1), super-
Figure 3. T2-weighted MR images of dogs that underwent embolization (upper row) and dogs that did not undergo embolization (bottom row) in group A. The three images were obtained before hormone treatment, 12 weeks after hormone injection (before embolization), and 12 weeks after embolization. The last images show the decreased size of the prostate in both dogs, without a significant difference associated with embolization.

Figure 4. T2-weighted MR images of dogs that underwent embolization (upper row) and dogs that did not undergo embolization (bottom row) in group B. The three images were obtained before hormone treatment, 12 weeks after hormone injection (before embolization), and 12 weeks after embolization. Serial images revealed continuous enlargement of the prostates. There are large cystic portions in the prostate of the embolized beagle (arrows).
selection of the prostatic branch failed. To protect the cystic branch, it was selected with a microcatheter and embolization was performed with microcoils (Tornado; Cook, Bloomington, Indiana; Fig 2). PVA particles were then injected through the inferior vesical artery to the prostate. Four of the prostates were supplied equally from both inferior vesical arteries. In one dog (dog no. 8), the right inferior vesical artery supplied most of the prostate and the left inferior vesical artery supplied only a small part of the left side of the prostate. All animals tolerated the entire procedure well and no immediate complications were noted.

**Pathologic Findings**

In group B, the weights of the prostates of all five dogs exceeded 14 g, which is consistent with prostate hyperplasia in dogs. Macroscopic examination of the prostate gland sections removed from the dogs revealed large cystic portions in the prostates of two dogs that underwent embolization, which is consistent with the MR findings (Fig 5). Under the microscope, the prostates of the dogs that underwent embolization showed cystic changes lined with regenerative epithelium and atrophied glands admixed with islands of normal glandular hyperplasia (Fig 6). Multifocal fibrosis with inflammatory cell infiltration and vessels containing embolic material were also demonstrated. All these findings were mainly present in the gland periphery. In the prostates of the nonembolized dogs, the main finding was diffuse glandular hyperplasia with microcyst formation (Fig 7). One specimen from a dog that did not undergo embolization showed focal hemorrhage.

In group A, mild glandular dilation with stromal hyperplasia was seen in the nonembolized dogs, whereas glandular atrophy and interstitial fibrosis were seen in the embolized dogs.

There were no gross or microscopic changes in the bladders, apart from focal hemorrhage in one specimen that did not involve the entire thickness of the wall. Even in this case, there were no changes in voiding pattern or urine color, nor was there gross hematuria. No gross damage to the surrounding colon or muscles was noted during examination while harvesting the prostates and bladders.

**DISCUSSION**

There have been reports on the effectiveness of transcatheter arterial embolization in controlling bleeding after prostatectomy or prostate biopsy and in pelvic malignancies (13–16). DeMeritt et al (17) reported that transarterial prostate embolization was effective not only in controlling bleeding, but also in the relief of BPH-related bladder outlet obstruction. In the present study, in group B, which was given hormones for 24 weeks, embolization could not prevent the further enlargement of the prostate. This seemed to result from the fact that, unlike in uterine fibroid embolization, the blood flow to the prostate was not completely occluded so as to result in infarction. That is, the blood perfusion to the prostate decreased, and the perfused hormones decreased. As a result, the overall prostate volume increase of the embolized dogs was smaller than in the nonembolized beagles. In this study, 250–355-μm PVA particles were used, which are larger than those used by DeMeritt et al (17). The authors thought a smaller PVA particle size might increase the possibility of bladder infarction and postembolization syndrome. However, the PVA particles were found in the peripheral prostate, which suggests that better re-
results may be achieved with smaller particles. Several complications secondary to internal iliac artery embolization have been reported, including gluteal pain, neurologic deficits, and bladder necrosis (15,23,24). No neurologic deficit was evident in any dog after embolization in the present study. The bladder was also grossly and microscopically evaluated. There was a focal bladder hemorrhage in one animal. However, even in this case, the hemorrhage did not involve the entire layer of the bladder wall. No other serious complications were seen.

In group B, prostate hyperplasia was induced in all dogs, as seen on pathologic examination. The microscopic findings of the nonembolized dog prostates showed diffuse gland hyperplasia and microcyst formation, which was consistent with a previous report (19).

Histologically, gland atrophy, fibrosis, and inflammatory cell infiltration were found in the prostates of the embolized dogs. Similar findings of lymphocyte and fibroblast infiltrations in interstitial tissue after embolization of the internal iliac arteries have been reported (18); these authors speculated that this occurred as a result of the reaction of the organ to ischemia. In a recent study of healthy pigs (25), microscopic examination showed fibrosis and atrophy of the gland consistent with the histologic findings of the present study. Zvara et al (26) reported that fibrosis and tissue shrinkage is the presumed mechanism for relieving obstructive symptoms. Another notable pathologic finding of the present study was the formation of large cysts in the prostates of embolized dogs. To the authors’ knowledge, there is no similar report of this finding after embolization. These large cysts were speculated to result from ischemic necrosis and re-epithelialization during the 12 weeks after embolization.

Animal studies of prostate hyperplasia are generally performed with dogs because, like humans, they develop prostatic disease such as hyperplasia or carcinoma spontaneously (27). Successful results of hormone-induced canine prostate hyperplasia have been reported for several decades (19–21). According to these reports, experimentally induced canine prostate hyperplasia was histologically indistinguishable from the spontaneous disease (21). With the reported methods, the present authors successfully induced BPH in dogs. Most previous reports focused on the hormonal effects on the development of prostate hyperplasia, and to our knowledge none examined changes in the prostate after discontinuation of hormones. Therefore, to distinguish between the effects of the hormones and embolization, the dogs in the present study were divided into two groups. Prostate size decreased after ceasing hormone injections in group A, regardless of embolization. For this reason, when evaluating the effect of treatment in hormone-induced prostate hyperplasia, hormone administration should be maintained until the end of the study.

There are several limitations to the present study. First, even though the results showed a trend toward a smaller prostate volume increase in embolized dogs in group B, there was no significant difference between the embolized and nonembolized groups ($P = .083$). However, the small sample size decreases the weight of the statistical result, and a larger sample size may have been associated with a significant difference. Second, the vol-
ume of the prostate was measured manually and there was a possibility of measurement error, even though there was strong positive agreement among the readers. Third, the symptoms of outflow obstruction in BPH in humans are caused by fibrostromal proliferation of the periurethral glands, with subsequent encroachment on the urethra. Unlike the situation in humans, the enlarging gland rarely causes urinary tract obstruction in dogs (22,27). Therefore, the present study cannot show the effect on BPH-related bladder outlet obstruction. To more accurately evaluate the effect on BPH, the direction of prostate growth may have to be controlled with another method, such as that reported by Broderick et al (22). Finally, sexual dysfunction after embolization could not be evaluated.

The present study showed that, in hormone-induced prostatic hyperplasia, the prostate is hypervascular, with supplying arteries sufficiently enlarged to be selected with use of a microcatheter. Transcatheter arterial embolization is feasible and reduced the prostate volume without serious complications in hormone-induced canine prostate hyperplasia. The authors believe the results warrant further preclinical study. Further study is needed to determine whether the prostate is also hypervascular in humans with BPH, whether it can be embolized, and whether the prostatic branches of the inferior vesical artery are sufficiently enlarged to be selected with use of a microcatheter.

References