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Therapeutic studies on benign prostatic hyperplasia in canines

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Abstract
The present study was conducted on 12 intact male dogs with clinical symptoms related to benign prostatic hyperplasia (BPH) and 12 apparently healthy intact male dogs presented to the Department of Veterinary Gynaecology and Obstetrics, Veterinary College, Hebbal, Bengaluru. Presumptive diagnosis was done based on history, clinical signs, digital rectal palpation of prostate and ultrasonographic measurement of prostatic volume. On haemato-biochemical analysis, TEC and PCV in BPH affected dogs were significantly lower compared to healthy dogs whereas other parameters did not vary between healthy and BPH affected dogs. Dogs with BPH were categorised into two treatment groups as Group I (n=6), treated with finasteride (0.1-0.5 mg/kg, SID, PO) and Group II (n=6) treated with flutamide (5 mg/kg, SID, PO) for 45 days. Dogs were re-examined on day 15, 30, 45 and 60 to evaluate response to the treatment. The results revealed that both medications were effective to resolve clinical signs and decrease prostatic volume.

Keywords: BPH, finasteride, flutamide, digital rectal palpation and ultrasonography

1. Introduction
The prostate gland is the sole accessory sex gland present in male dogs. It is having a spherical and bilobed structure that encircles the proximal urethra. Prostatic disorders are most commonly observed in older intact dogs and the most common prostatic disease encountered is the benign prostatic hyperplasia (BPH) [3].

BPH is a part of an aging process, including both an increase in prostatic epithelial cell number (hyperplasia) and an increase in prostatic cell size (hypertrophy) [19]. More than 80% of intact male dogs > 5 years old and > 95% dogs >9 years old develop BPH [13, 25].

BPH begins with change in androgen: estrogen ratio that is secreted by the testes [2]. The prostate shows continual, androgen-dependent growth that is sensitive to estrogens which increases androgen receptors in prostate. The testosterone from testicular tissue gets converted to dihydrotestosterone by 5-alpha-reductase enzyme in the prostate, which interacts with androgen receptors causing prostatic growth [7].

The dogs with BPH are asymptomatic, if present in dogs with BPH, the most common is the serous to sanguineous urethral discharge [23]. Sometimes the sanguineous discharge from prostate enters urinary bladder and results in haematuria. Because of hyperplastic prostate or large intraparenchymal cysts in BPH, tenesmus, dischezia, constipation and rarely dysuria, incontinence and strangury could occur. Caudal abdominal pain and infertility also could be observed.

Presumptive diagnosis could be made by history, clinical examination and prostatic imaging techniques like ultrasonography and radiology [26] and response to treatment could also be considered to arrive at a presumptive diagnosis. A definitive diagnosis could be established by biopsy and histopathology [14].

The suggested permanent treatment for non-breeding male dogs with BPH is castration [14], as it removes androgen influence for prostate gland enlargement [25]. For valuable breeding dogs or in BPH dogs with prostatitis with an abscess or dogs having higher risk in anaesthesia medical treatment should be considered [14]. The pharmacological treatments more frequently recommended in literature are: 5α-reductase inhibitors (Finasteride), inhibitors of androgen receptors (Flutamide and Osaterone acetate), androgen antagonists (progestogens), GnRH analogs (deslorelin acetate) and antiestrogen therapies (Tamoxifen) and aromatase inhibitors (such as anastrozole) [22, 26].

2. Materials and Methods

2.1 Selection of animals

Twelve male dogs presented to clinics of different age (2 to 10 years) and different breeds showing one or more clinical symptoms suggestive of BPH were considered and subjected for general clinical examination, digital rectal palpation of prostate and ultrasonography of prostate to confirm the condition. Blood samples were collected for haemato-biochemical parameters analysis.

Twelve intact male dogs were subjected for general clinical examination, digital rectal palpation of prostate and ultrasonography of prostate gland. Based on history, preliminary examination, apparently healthy male dogs with normal prostate echography findings were taken as control group for comparison. Blood samples were collected for haemato-biochemical parameters analysis.

2.2 Diagnosis of BPH

Diagnosis of BPH in each dog was based on history, clinical examination, digital rectal palpation of prostate and ultrasonography of prostate gland.

2.2.1 History and description of animal

Details like breed of the animal, age, clinical history regarding appetite, duration of illness, abnormal gait, dysuria, colour of urine, constipation and loss of body condition were collected from the owner.

2.2.2 Digital rectal palpation (DRE) of prostate gland

After general examination of dogs, the prostate of each animal was palpated rectally in standing position using a gloved, lubricated finger and observation regarding location of the prostate, consistency, symmetry, mobility and presence or absence of pain were recorded.

2.2.3 Ultrasonography of prostate gland

Ultrasonography was done using ultrasound machine (Aloka-Prosound α6, Hitachi Aloka Medical, Ltd., Tokyo, Japan) using a 5 to 7.5 MHz transabdominal probe**.** For imaging the prostate gland, the dog was positioned in dorsal or lateral recumbency, the probe was placed against the ventral abdominal wall cranial to the pubis, on one side of the penis or prepuce after application of coupling/transmission gel to improve contact. A distended urinary bladder was preferred as it pulls the prostate cranially for better visualization. Trigone of urinary bladder was used as landmark to locate prostate gland.

To measure the actual volume of the prostate, length (sagittal), width (transverse) and height (both transverse and sagittal) of the prostate were measured. Accurate sagittal views were confirmed by visualising the hypoechoic urethral tract. Actual volume of the prostate gland was measured using double B mode.

B mode in ultrasonography showing both transverse (left) and sagittal (right) section of the prostate (note the hypoechoic urethral tract)

The normal expected prostatic volume was estimated with respect to dog's weight using following formula:

Expected prostate volume (cm^3) = (0.33 X body weight (Kg) +3.28) [24].

Volume ratio (V-ratio): actual prostate volume (by ultrasonography) /normal expected prostatic volume [1, 11].
V-ratio ≥ 1.5 was taken as suggestive of BPH [1].

2.3 Treatment group

The male dogs diagnosed with BPH were randomly allotted to the following two treatment groups with six dogs in each.

Group I: Dogs with BPH were treated with finasteride for 45 days at the dose rate of 0.1-0.5 mg/kg, PO, SID (Tab. Finax™-1 mg and Tab. Finast®-5 mg, Dr. Reddy's Laboratories Ltd., Haridwar, Uttarakhand).

Group II: Dogs with BPH were treated with flutamide for 45 days at the dose rate of 5 mg/kg, PO, SID (Tab. Cytomid-250 mg, Cipla Ltd., Goa, India).

2.4 Evaluation of the therapeutic efficacy of different treatments

All dogs in two different treatment groups were re-examined on 15th day, 30th day, 45th and 60th day after the initiation of treatment for the clinical evidence of resolution of BPH. Following general clinical examination, digital rectal palpation of prostate and ultrasonography of the prostate were carried out to see the response to the treatment.

2.5 Statistical analysis
Percentage change in prostate volume on day 15, 30, 45 and 60 relative to day 0 were compared by one way ANOVA. All the results were statistically analysed using computer based statistical programme, GraphPad Prism 5.0 and interpreted as per the procedure described by Snedecor and Cochran, (1996) [28].

3. Results and Discussion
3.1 Clinical history of dogs with BPH
In BPH affected dogs, clinical signs related to BPH included constipation in seven out of 12 dogs (7/12, 58.33%), passing ribbon like feces (7/12, 58.33%), tenesmus (6/12, 50%), haematuria (5/12,41.67%), loss of body condition (4/12, 33.33%), dysuria (3/12, 25%), haemorrhagic prepucial discharge (3/12, 25%) and gait abnormality (2/12, 16.67%). Almost similar observations were recorded by Socha *et al.* (2018) [27] who reported that constipation and tenesmus were observed in 69.6% of the dogs with BPH. Davidson (2003) [6] and Holt (2007) [12] stated that the constipation characterized by tenesmus was one of the prominent clinical signs seen in dogs with BPH due to compression of colon by the hyperplastic prostate gland which interferes with defecation leading to constipation and rectal tenesmus which correlates with the predominant symptom observed in this study too.
Almost similar results were obtained by Das *et al.* (2017) [5] who observed 45.6% of dogs exhibited hematuria and 26.3% of dogs exhibited loss of body condition. Gait abnormality, urination related problems, urethral blood discharge were observed in 56.5%, 52.1% and 47.8% of the patients with BPH [27].

3.2 Haemato-biochemical parameters of control group and dogs with BPH
The mean values of haematological parameters like Total Erythrocyte Count, Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC), Haemoglobin (Hb), Packed Cell Volume (PCV) and Total platelet count and serum biochemical parameters like Blood Urea Nitrogen (BUN) and creatinine of control group and dogs with BPH were found to be within the normal physiological range (Table 1). However, TEC and PCV in the BPH affected dogs were found to be significantly lower compared to control group, whereas other parameters did not vary significantly.
Similar results were obtained by Khaki *et al.* (2017) [16] who recorded no significant differences in WBC counts, Hb concentration, DLC and serum biochemical parameters. Gautam *et al.* (2019) [9] has also found normal haemogram in 19 dogs with prostate affections.
It is also in similar accordance with the reports of Das *et al.* (2017) [5] and Konwar *et al.* (2017) [8] in dogs with prostatic hyperplasia. The reduction of packed cell volume values might be because of haematuria and also due to urinary obstruction by the enlarged prostate resulting in chronic kidney disease that led to reduced erythropoietin production and reduced capacity of bone marrow to produce RBCs, which in-turn causes lower total erythrocyte count production (Das *et al.*, 2017) [5].

Table 1: Haemato-biochemical parameters of control group and dogs with BPH

Sl. No.	Parameter	Control (n=12)	BPH (n=12)	Significance
1.	TEC (10^6cells/mm^3)	7.43±0.18	6.69±0.29	*
2.	TLC (10^3cells/mm^3)	12.75±0.62	12.17±0.99	ns
3.	Neutrophils (%)	69.95±2.17	72.47±3.62	ns
4.	Lymphocytes (%)	21.50±1.74	17.44±1.44	ns
5.	Monocytes (%)	6.60±1.20	6.35±2.91	ns
6.	Eosinophils (%)	2.36±0.90	2.60±0.75	ns
7.	Haemoglobin (g%)	16.62±0.55	15.42±0.49	ns
8.	PCV (%)	48.68±0.96	42.27±1.42	**
9.	Total platelet count (10^9/L)	260.40±20.59	299.50±48.59	ns
10.	BUN (mg/dL)	13.53±1.53	19.42±3.13	ns
11.	Creatinine (mg/dL)	1.22±0.09	1.42±0.28	ns

Note: * - Significant at $p<0.05$; ** - Significant at $p<0.01$; ns - non significant

3.3 Clinical efficiency
3.3.1 Effect of treatment on prostate volume of dogs with BPH
In Group I and Group 2 dogs, the mean value of the actual prostate volume before the treatment and after the treatment were given in Table 2. The mean percentage reduction in the prostate volume on day 15, day 30, day 45 and day 60 relative to day 0 are shown in Figure 1 and reduction in prostate volume was found to be significant.
Johnston *et al.* (2001) [14] and Sirinarumitr *et al.* (2001) [25] reported similar results and recorded nearly one-half (43%) of reduction of prostate size in dogs with BPH treated with finasteride at the dose of 0.1 mg/kg orally once per day (not to exceed 5 mg per day per dog) for 16 weeks. In the earlier work on canine hyperplasia by Neri and Monahan (1972) [21] and Geller *et al.* (1981) [10] who reported that flutamide continued to decrease prostate size up to six months significantly and in some cases, for up to a year.

Table 2: Effect of treatment on prostate volume of dogs with BPH

Sl. No.	Group	Prostate volume (0^{th} day)	Prostate volume (45^{th} day)	Significance
1	Finasteride (n=6)	31.60±5.11	12.96±2.09	**
2	Flutamide (n=6)	24.36±5.78	8.31±1.51	*

Note: * - Significant at $p<0.05$; ** - Significant at $p<0.01$

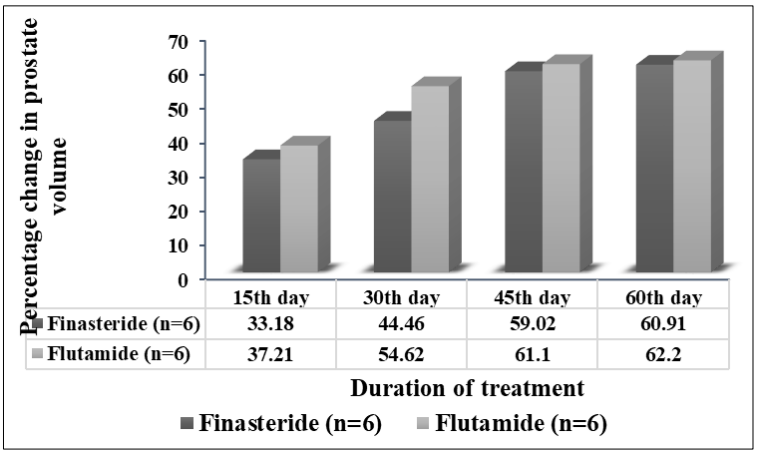

Fig 1: Relative mean percentage change in the prostate volume following treatment

3.3.2 Resolution of clinical symptoms in dogs with BPH after the treatment

In Group I, all six dogs were active, alert, having normal appetite, normal urination and defecation after 45 days of finasteride treatment. All the symptoms observed at the time of presentation were resolved.

These findings are in accordance with observations of Sirinarumitr *et al*. (2001) [25] and Das *et al.* (2017) [5] who noted that finasteride treatment was effective to reduce prostatic size, to resolve clinical signs and had no effect on semen quality, libido except to reduction in semen volume. Nagabhushan (2019) [20] worked on treating canine BPH by finasteride and reported that all the clinical signs observed at the time of presentation of the case were resolved at the end of observation period (45 days).

In Group II dogs, out of six dogs treated with flutamide, two dogs showed adverse effects like vomition and inappetence for 2 days at the beginning of treatment. After 45 days of treatment all six dogs were active, alert, having normal appetite, normal urination and defecation. All the symptoms observed at the time of presentation were resolved.

No similar studies were reported in canines but in report by Kassem and Neri (1982) [15] stated that with flutamide monotherapy for prostate cancer in humans, nausea and vomiting were the most common adverse effects. Chojnacka *et al.* (2016) [4] stated that transient hepatic enzyme elevation was one of the reasons quoted for the adverse effects in flutamide treatment in one of the human studies.

4. Conclusion

In conclusion, in the current study, the clinical signs, digital rectal palpation of prostate and ultrasonographic measurement of prostate volume were effective in diagnosis of canine BPH. Effective clinical outcome with resolution of clinical signs recorded at the time of presentation of case and reduction of prostate volume were found in both Group I and II dogs. It can be concluded that both finasteride and flutamide were efficient in treating the canine BPH.

5. References

1. Alonge S, Melandri M, Aiudi G, Lacalandra GM. Advances in prostatic diagnostics in dogs: The role of canine prostatic specific esterase in the early diagnosis of prostatic disorders. Top Companion Anim Med. 2018;3(4):105-108.
2. Bamberg-Thalen BL, Linde-Forsberg C. Treatment of canine benign prostatic hyperplasia with medroxyprogesterone acetate. J Am Anim Hosp Assoc. 1993;29(3):221-226.
3. Bauzaite N, Aniuliene A. Enlarged prostate lesion of pure-bred and mongrel dogs. Med Weter. 2003;59:686-690.
4. Chojnacka K, Hejmej A, Zarzycka M, Tworzydlo W, Bilinski S, Pardyak L, *et al*. Flutamide induces alterations in the cell-cell junction ultrastructure and reduces the expression of Cx43 at the blood-testis barrier with no disturbance in the rat seminiferous tubule morphology. Reprod Biol Endocrinol. 2016;14(1):1-13.
5. Das MR, Patra RC, Das RK, Rath PK, Mishra BP. Hemato-biochemical alterations and urinalysis in dogs suffering from benign prostatic hyperplasia. Vet World. 2017;10(3):331-335.
6. Davidson JR. Prostatic diseases of the dog, Waltham Focus. 2003;13(2):4-10.
7. Fontbone A. Infertility in male dogs: recent advances. Rev Bras Reprod Anim. 2011;35:266-273.
8. Konwar B, Kalita D, Sarma KK, Rao GD, Gogoi D, Dutta D, *et al*. Diagnosis of canine prostatic hyperplasia and cyst. Int J Curr Adv Res. 2017;9:61572-61576.
9. Gautam A, Sharma AK, Saxena AC, Kumar N, Gautam D, Verma N. Prostate affections in dogs: incidence and clinical analysis. J Entomol Zool Stud. 2019;7:413-417.
10. Geller J. Pathogenesis and medical treatment of benign prostatic hyperplasia. Prostate. 1989;15:95-104.
11. Holst BS, Holmroos E, Friling L, Hanas S, Langborg LM, Franko MA, *et al*. The association between the serum concentration of canine prostate specific esterase (CPSE) and the size of the canine prostate. Theriogenology. 2017;93:33-39.
12. Holt PE. Prostate disease. In: SEVC (Southern European Veterinary Conference) Proceedings, International Veterinary Information Service, Ithaca, New York. 2007.
13. Johnston SD, Kamolpatana K, Kustritz MVR, Johnston GR. Prostatic disorders in the dog. Anim Reprod Sci. 2000;60-61:405-415.
14. Johnston SD, Root Kustritz MV, Olson PNS. Disorders of the canine testes and epididymes. In: Canine and feline theriogenology, Edn. 1st., W. B. Saunders, Philadelphia, 2001,312-332.
15. Kassem NY, Neri RO. Flutamide in advanced cancer of the prostate. Clin Pharmacol Ther. 1982;31(57):238-241.
16. Khaki Z, Masoudifard M, Khadivar F, Shirani D,

Fathipour V, Taheri M. Serum biochemical and hematological parameters in dogs with benign prostatic hyperplasia (BPH). Iran J Vet Med. 2017;11(1):55-62.
17. Konwar B, Kalita D, Sarma KK, Rao GD, Gogoi D, Dutta D, *et al*. Diagnosis of canine prostatic hyperplasia and cyst. Int J Curr Adv Res. 2017;9:61572-61576.
18. Krawiec DR, Heflin D. Study of prostatic disease in dogs: 177 cases (1981-1986). J Am Vet Med Assoc. 1992;200:1119-1122.
19. Kutzler M, Yeager A. Prostatic diseases. In: Textbook of veterinary internal medicine, Edt. Ettinger. Edn. 6th., W. B. Saunders, Philadelphia, 2005, 1809-1819.
20. Nagabhushan K. Studies on efficacy of imaging techniques and biomarkers in diagnosis of canine prostatic affections and their management. M. V. Sc. Thesis, Sri Venkateswara Veterinary University, Tirupati, India, 2019.
21. Neri RO, Monahan M. Effects of a novel nonsteroidal anti-androgen on canine prostatic hyperplasia. Invest Urol. 1972;10:123-130.
22. Nizanski WO, Levy X, Ochota M, Pasikowska J. Pharmacological treatment for common prostatic conditions in dogs: benign prostatic hyperplasia and prostatitis: an update. Reprod Domest Anim. 2014;49(2):8-15.
23. Read RA, Bryden S. Urethral bleeding as a presenting sign of benign prostatic hyperplasia in the dog: a retrospective study (1979-1993). J Am Anim Hosp Assoc. 1995;31:261-267.
24. Sannamwong N, Saengklub N, Sriphuttathachot P, Ponglowhapan S. Formula derived prostate volume determination of normal healthy intact dogs in comparison to dogs with clinical BPH. In: 7th International Symposium on Canine and Feline Reproduction, July 26-29th 2012, Whistler. 2012, p. 226-231.
25. Sirinarumitr KJ, Johnston SD, Root Kustritz MV, Johnston GR, Sarkar D, Memon MA. Effects of finasteride on size of the prostate gland and semen quality in dogs with benign prostatic hypertrophy. J Am Vet Med Assoc. 2001;218(8):1275-1280.
26. Smith J. Canine prostatic disease: A review of anatomy, pathology, diagnosis and treatment. Theriogenology. 2008;70:375-383.
27. Socha P, Zduńczyk S, Tobolski D, Janowski T. The effects of osaterone acetate on clinical signs and prostate volume in dogs with benign prostatic hyperplasia. Pol J Vet Sci. 2018;21(4):797-802.
28. Snedecor GW, Cochran WG. Statistical methods. Fifth edition. Ames, Iowa; Iowa State University Press; c1996.