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RESEARCH ARTICLE
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DOSE-DEPENDENT EFFECTS OF TAMSULOSIN ON TESTICULAR HISTOLOGY AND REPRODUCTIVE FUNCTION

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ABSTRACT

Introduction: Tamsulosin, an α1A-adrenoceptor antagonist commonly used for lower urinary tract symptoms, may affect male reproductive function by altering testicular microarchitecture. Understanding its dose-dependent impact on seminiferous tubules and interstitial cells is essential for evaluating reproductive safety.

Objective: To investigate the dose-dependent effects of tamsulosin on testicular histology and function, focusing on structural changes within seminiferous tubules and interstitial compartments.

Methodology: Thirty adult albino mice were divided into three groups: control, low-dose (8 µg/kg/day), and high-dose (16 µg/kg/day) tamsulosin, administered for 45 days. Testes were collected, fixed, processed, and stained with hematoxylin and eosin for histopathological evaluation. Seminiferous tubule integrity, germ cell maturation, Leydig cell count, and tunica albuginea thickness were assessed using standardized Johnsen scoring. Data were analyzed with ANOVA and Tukey post hoc tests.

Results: Control testes showed preserved seminiferous architecture with complete spermatogenesis. Low-dose tamsulosin induced mild disorganization of germinal epithelium, while high-dose exposure caused marked degeneration of seminiferous tubules, spermatogenic arrest, and altered interstitial Leydig cell populations. Johnsen scores were significantly reduced in the high-dose group ($p \leq 0.05$), whereas tunica albuginea thickness remained unchanged.

Conclusion: Tamsulosin induces dose-dependent testicular histopathological alterations, with higher doses producing significant seminiferous tubular degeneration and interstitial cell changes. These findings highlight the importance of histological evaluation in assessing the reproductive safety of α1A-adrenoceptor antagonists.

Keywords: Tamsulosin, Testicular histology, Johnsen score, Leydig cells, Spermatogenesis

INTRODUCTION

Lower urinary tract symptoms (LUTS) resulting from benign prostatic hyperplasia (BPH) are common in the elderly with their incidence increasing with age. Therefore, placing a significant burden on healthcare systems.[1,2] The chestnut-shaped prostate gland, measuring approximately 4×3×2 cm, lies above the urogenital diaphragm and below the urinary bladder, through which the urethra traverses upon exiting the bladder. It is anatomically divided into five lobes namely anterior, middle, posterior, and two lateral lobes without clear boundaries. Changes characteristic of BPH primarily affect the middle lobe, and prostatic fluid constitutes 37-44% of a single male ejaculate.[3] The testes, as the primary producers of testosterone, are supplemented by the zona reticularis of the adrenal cortex, which releases prohormones such as DHEA and DHEA-S that can be converted into testosterone alongside their own physiological functions.[4] However, with aging, there is a reduction in the quantity of Leydig cells and Sertoli cells, leading to an increased mass of the tunica albuginea of the testes due to a relative insufficiency of testosterone.[5]

Tamsulosin specifically targets and blocks the alpha-1A receptors in the prostate. It stands as the third uroselective alpha-1A receptor antagonist, exhibiting a 10-fold higher selectivity for receptor subtype A in comparison to subtype B.[6] At the microscopic level, BPH involves noradrenergic receptors, classified into GPCR (G protein-coupled receptor) alpha and beta variants, with alpha receptors further divided into alpha-1 and alpha-2 types. The alpha-1 subgroup has three recognized variants 1A,1B and 1D based on differences in their amino acid configuration. Alpha-1 adrenoceptors predominantly attach to G proteins and stimulate the enzyme phospholipase C, which cleaves cellular phospholipids into inositol triphosphate (IP3) and diacylglycerol (DAG).These secondary signals amplify intracellular calcium levels and activate protein kinase C (PKC), facilitating the relaxation of smooth muscle.[7]

The substrates facilitating smooth muscle relaxation, particularly concerning alpha-1A adrenergic receptors, are predominantly located within the smooth muscle of the prostate gland, testis, testicular capsule, seminal vesicle, and epididymis, and to a lesser extent within the vascular system in both humans and mice. Molecular investigations reveal that the alpha-1A subtype constitutes 70% of alpha receptors in the prostate gland.[8] These receptors are significant not only in the prostate and bladder neck but also in the vascular system, with tamsulosin HCl demonstrating increased selectivity for alpha-1 receptors in the prostate while exerting negligible influence on those within blood vessels.[9]

Tamsulosin concentration-dependently inhibits noradrenaline-induced contraction in seminal vesicles, vas deferens, bladder trigon, prostate, as well as the detrusor and ureter, potentially aiding in the expulsion of minor calculi from the terminal parts of the ureters. It is a potent drug with minimal side effects, suitable for treating both BPH and prostatic cancer.[10] Tamsulosin is approved by the FDA for the treatment of symptoms of bladder outlet obstruction (BOO) associated with BPH. It is the most frequently prescribed medication for alleviating urinary tract symptoms, with a minimal to no side effect profile for short-term use. However, long-term usage can result in adverse effects such as headache, asthenia, chest pain, back pain, rhinitis, and pharyngitis, exacerbation of cough, sinusitis, ejaculatory dysfunction, dizziness, sleep disturbances, nausea, diarrhea, tooth disorders, blurred vision, and orthostatic hypotension.

A primary concern with prescribing tamsulosin is its impact on male sexual function, specifically causing retrograde ejaculation, where semen is rerouted back into the urinary bladder due to improper contraction of the sphincter between the bladder and urethra.[11]Inhibiting alpha-1A receptor activity also shows a direct contraceptive effect in experimental rodents, accompanied by marked ejaculatory dysfunction[12]. Alpha-1A receptor blockers have a high binding affinity for several other receptors, including dopamine and serotonin. The contraceptive effect of alpha-1A receptor antagonists likely stems from their central influence on dopamine and serotonin receptors, as well as reduced serum testosterone levels at higher doses.[13]Alpha-1 adrenoceptor antagonists cause sperm retention in the tail of the epididymis, thereby reducing the number of sperm in the vaginal canal.[14] The anti-infertility effects of tamsulosin do not significantly affect libido and mating performance in mice. Thus, while tamsulosin is effective in treating BPH, the potential adverse

effects on fertility warrant careful consideration. This research aims to elucidate the morphological impacts of the drug on the testes, assessing both its direct anti-fertility effects and any indirect effects on the genital system. From a pathological perspective, disruption of androgen-dependent signaling and α1A-adrenoceptor activity may adversely affect the testicular microenvironment, leading to altered spermatogenesis and interstitial cell dynamics. Histological evaluation provides critical insight into drug-induced reproductive toxicity beyond functional clinical outcomes.

METHODOLOGY

Study Design: It was an experimental study.

Ethical Approval: The study, approved by the Ethical Review Board of the University of Health Sciences, Lahore, utilized a mouse model to prioritize patient safety and avoid ethical concerns related to human studies.

Inclusion criteria: 30 adult male albino mice (BALB/C), 25-35 grams, 11-13 weeks old, acquired from National Institute of Health, Islamabad.

Exclusion criteria: Mice showing any signs of disease or dead during the study were to be excluded, but none showed such signs.

Mice Groups: The 30 mice were divided into three groups: A, B, and C, with 10 mice in each group. Group A (control group) received only food and water, while Groups B and C, each consisting of 10 mice, were administered the drug Tamsulosin.

Dissection: 24 hours after the final drug dose, the animals were dissected under chloroform anesthesia.An inverted T-shaped incision was made, the testes were exposed, removed, cleaned, weighed, and sectioned for further examination. The animals were then euthanized by decapitation. This protocol ensured proper tissue fixation, dehydration, embedding, sectioning, and staining for detailed histological analysis. For histopathological assessment, testes were fixed, processed, sectioned, and stained with hematoxylin and eosin. Seminiferous tubules were evaluated for epithelial organization, germ cell maturation, and interstitial changes using standardized Johnsen scoring criteria.

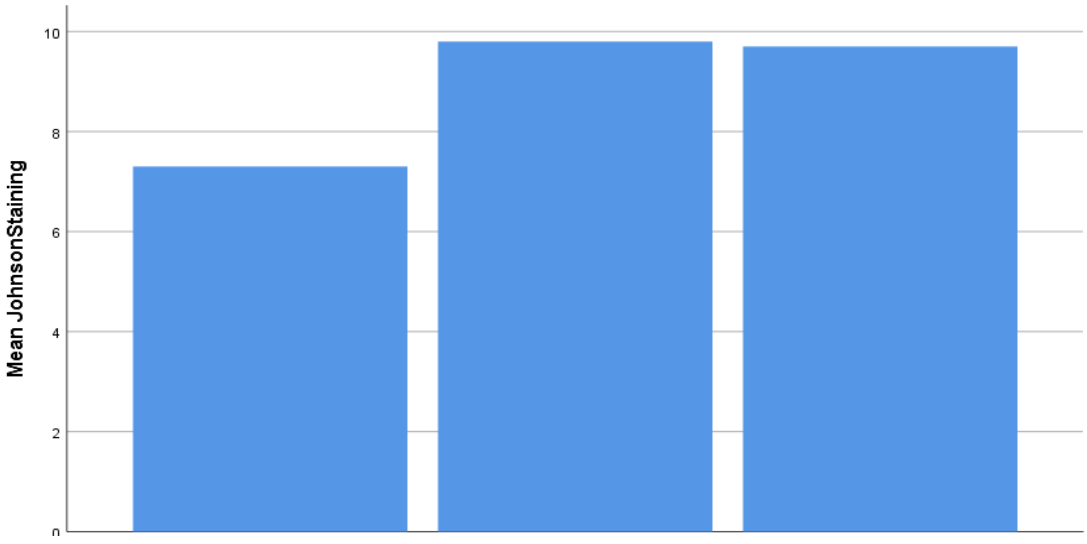
Data Analysis: Data analysis was performed using SPSS 22.0. Means and standard deviations were calculated for all continuous variables, and a *p*-value was determined to assess significance. A one-way ANOVA was used to obtain the *p*-value, with $p \leq 0.05$ considered significant. For statistically significant results, a Post Hoc Tukey test was applied.

RESULTS

The study included 30 animals, which were divided into three groups labelled A, B, and C.

1. Johnsen Scoring:

The average Johnsen score was 8.93, with a range of 6 to 10.



Graph 1: Bar graph illustrating the comparison of average Johnsen scores among the three study groups (A, B, C)

Microscopic examination revealed preserved seminiferous tubular architecture in controls, while treated groups exhibited dose-dependent degeneration of germinal epithelium. High-dose exposure resulted in spermatogenic arrest and significant interstitial Leydig cell alterations, consistent with reduced Johnsen scores.

Table 1: Groupwise Johnsen Score

Groups	Mean	Standard Deviation	Minimum	Maximum	*p*-value
Group A	9.8	0.422	9	10	0.000*
Group B	9.7	0.483	9	10	
Group C	7.3	1.059	6	9	

Table II: Leydig cell count among different groups

Groups	Mean (n)	Standard Deviation (n)	Minimum (n)	Maximum (n)	*p*-value
Group A	156.7	54	72	224	0.007*
Group B	317	159	114	650	
Group C	224	66.5	88	304	

The Post Hoc Tukey test indicates a significant increase in the number of Leydig cells in the slide preparations for group C (receiving a higher dose) compared to group A(control).

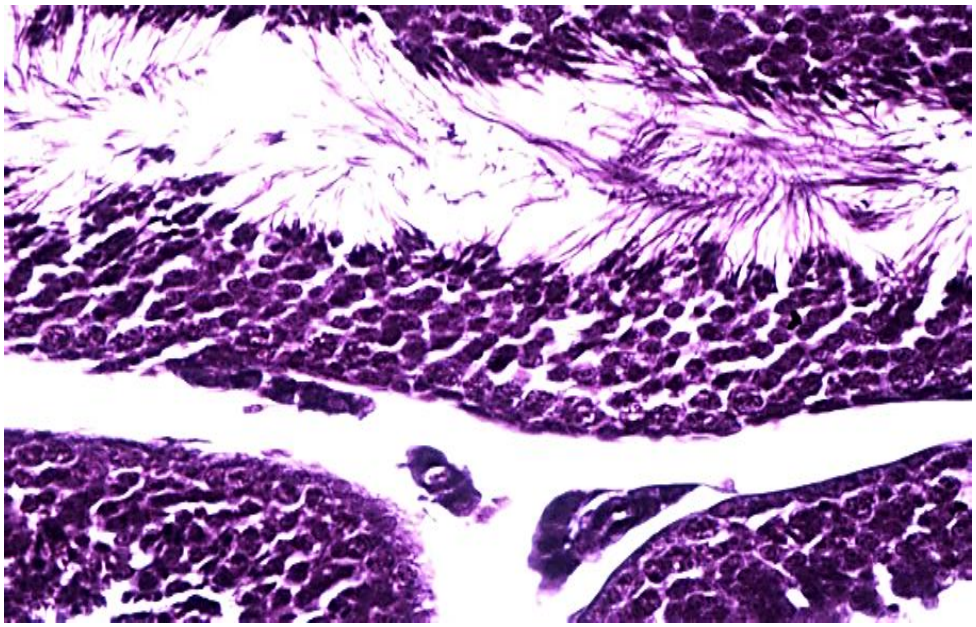


Figure 1: A photomicrograph displaying a testicular cross-section from group A exhibits a Johnsen score of 10, stained with hematoxylin and eosin at 40X magnification.

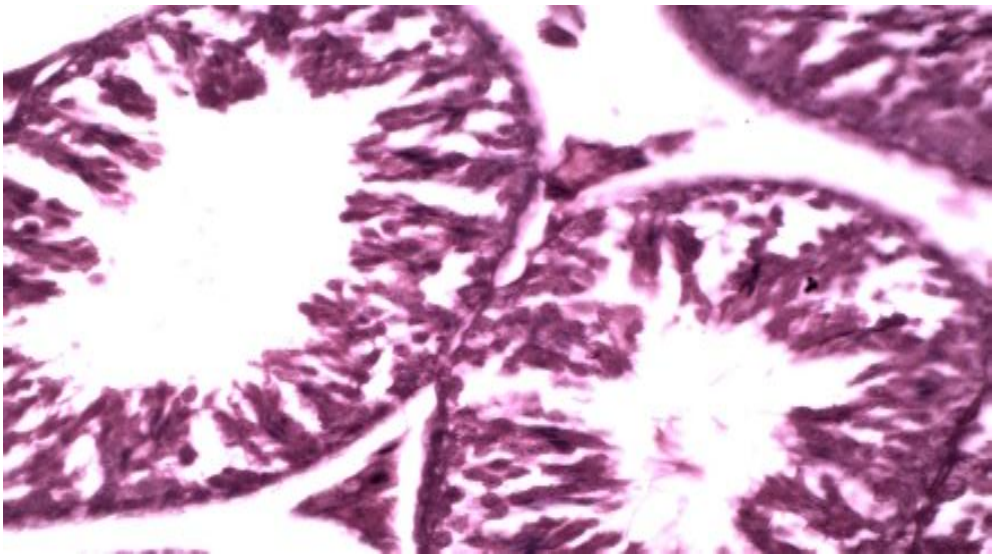


Figure 2: A photomicrograph of a testicular section from group B reveals a Johnsen score of 8, captured using hematoxylin and eosin staining at 40X magnification.

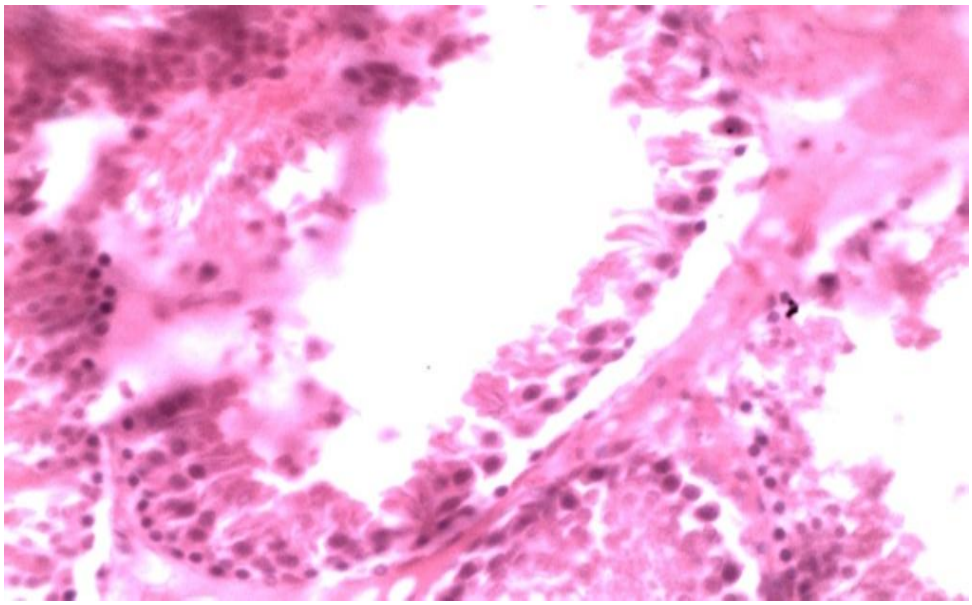


Figure 3: Photomicrograph showing testicular section from group C with a Johnsen scoring of 4. Hematoxylin and eosin, 40X.

The research revealed significant impacts of Tamsulosin on various parameters including Johnsen scoring, and Leydig cell count in mice administered the drug, particularly at higher doses (16µg/kg body weight) compared to lower doses (8µg/kg body weight) over a 45-day period. The findings indicated adverse effects on Johnsen scoring in both dosage groups receiving the drug compared to a control group. Notably, an increase in Leydig cell count was observed only in the group receiving the higher dose of the drug.

Moreover, studies indicate that α1-adrenoceptor blockers like Tamsulosin may affect ejaculatory function through various pathways, including interactions with dopamine and serotonin receptors, potentially leading to decreased ejaculatory volume and sperm concentration. However, discrepancies exist regarding the direct effects of Tamsulosin on testicular histology and Leydig cell counts, as observed in this study compared to previous research.

Importantly, while the study was conducted in mice, extrapolating these results to humans requires careful consideration due to differences in spermatogenesis and reproductive physiology. Nonetheless, murine models remain valuable for understanding initial effects on living organisms,

including humans, given the similarities in basic genital tract structure and α- adrenoceptor distribution.

The study sheds light on the potential cytotoxic effects of Tamsulosin on testicular histology in mice, highlighting the need for further research to elucidate the precise mechanisms and implications for human reproductive health. Future studies should explore hormonal dynamics underlying spermatogenesis and correlate them with anatomical changes to provide a comprehensive understanding of impact of Tamsulosin on the male reproductive tract.

DISCUSSION

The current mouse study demonstrates a dose-dependent reduction in seminiferous tubule integrity, reflected by lower Johnsen scores, along with an unexpected increase in Leydig cell numbers at higher tamsulosin doses, which shows only partial consistency with previous animal research and clinical pharmacological findings.

The observed seminiferous tubular degeneration reflects impaired spermatogenic activity, a hallmark pathological indicator of testicular toxicity. Increased Leydig cell counts at higher doses may represent a compensatory or hyperplastic response to disrupted endocrine regulation rather than functional recovery.

Multiple rodent studies have documented testicular histological alterations following long-term α1-adrenoceptor blockade—such as decreased testicular weight, thinning of the germinal epithelium, and reduced spermatogenic cell counts findings that correspond with the present study's observation of lower Johnsen scores after tamsulosin exposure.[15] In contrast, previous studies have more commonly reported a reduction in Leydig cell numbers or compromised steroid genesis following tamsulosin treatment. Therefore, the observed increase in Leydig cell counts in the present study appears unusual and may indicate either a compensatory hyperplastic response to diminished steroid production or methodological differences among studies, such as variations in staining techniques, counting fields, or sampling intervals.[16] Mechanistically, α1-adrenoceptor blockade may influence peritubular myoid cell contractility, epididymal transit, vas deferens activity, and testicular blood flow, leading secondarily to disturbances in spermatogenesis and semen emission. Recent studies further associate systemic α1 inhibition with reduced sperm quality and increased testicular oxidative stress in aging and disease models, offering a plausible explanation for the seminiferous damage observed in this study. Clinically, tamsulosin's known effects on ejaculatory volume reduction and retrograde ejaculation align with its impact on smooth muscle within the reproductive tract, although direct evidence from human testicular histology remains unavailable. [17]

Limitations: The absence of stereological analysis and hormonal correlation limits precise interpretation of Leydig cell hyperplasia versus hypertrophy. Incorporation of immunohistochemical and ultrastructural techniques would strengthen pathological interpretation. Variations in animal species or strain, dose scaling, route and duration of drug administration, and the timing of tissue collection relative to dosing may all contribute to differing outcomes across studies. Notably, this study did not assess compensatory endocrine parameters (LH, FSH, testosterone), which could help determine whether the observed increase in Leydig cells reflects a functional compensatory mechanism or merely nonfunctional hyperplasia. Future investigations should integrate histomorphometric evaluation with serum hormone profiling, stereological quantification of Leydig cells, and assessment of oxidative stress markers to better reconcile these findings and enhance their translational relevance for men undergoing long-term α1A-adrenoceptor blocker therapy.

CONCLUSION

The present findings indicate that tamsulosin exerts dose-dependent pathological effects on testicular histology, with higher doses leading to significant disruption of spermatogenesis and interstitial cellular alterations. While effective in managing lower urinary tract symptoms, prolonged exposure may pose risks to testicular structure and function. Continued experimental and clinical investigations integrating histological and hormonal assessments are essential to ensure reproductive safety during long-term therapy.

Conflict of Interest: None
Funding Sources: None

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