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Acute Effect of Ciprofloxacin on Sperm Concentration and Quality in Adult Male Wistar Rats

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Abstract

This study evaluated the short-term effects of ciprofloxacin on sperm concentration, morphology, motility and testicular structure in adult male rats. Fifteen rats were assigned to control, low-dose, and high-dose groups and treated orally for four days. Sperm parameters were analyzed using standard microscopic techniques, and testes were examined histologically. Ciprofloxacin increased sperm concentration and reduced the incidence of selected morphological defects in a dose-dependent manner, while motility shifted toward slower progressive movement. Histology revealed dose-related distortion of seminiferous architecture. These findings show that brief ciprofloxacin exposure enhances certain sperm characteristics while inducing structural testicular stress.

Keywords: Ciprofloxacin; histology; male fertility; sperm concentration; sperm motility

Introduction

Male reproductive health has undergone a significant global decline over the past several decades. Several epidemiological studies have reported a marked reduction in semen quality, including a 50-60% decrease in sperm concentration between 1973 and 2011 (Levine *et al.*, 2017; Sweeney *et al.*, 2019; Jørgensen *et al.*, 2001) [16, 25]. This decline is largely attributed to environmental exposures, endocrine-disrupting chemicals, and the frequent misuse of various drugs (Gore *et al.*, 2015; Kristensen *et al.*, 2016) [8]. Such factors may disrupt hormonal regulation, impair spermatogenesis, or directly induce oxidative damage to germ cells. Spermatogenesis is a highly organized process that takes place within the seminiferous tubules of the testes and is essential for the continuous production of viable spermatozoa (O'Donnell *et al.*, 2011) [21]. In humans, this process spans approximately 64 days, with millions of spermatozoa produced daily to support male fertility (Amann & Howards, 1980) [3]. The resulting sperm count, typically expressed in millions per milliliter, is a major determinant of male reproductive capacity, with values above fifteen million per milliliter considered normal by the World Health Organization (WHO, 2010) [28]. Disruptions in this process may lead to decreased sperm number, impaired motility, and increased morphological abnormalities, all of which contribute to malefactor infertility. Infertility affects an estimated 15% of couples worldwide, representing a substantial global health burden with significant emotional, psychological, and socioeconomic consequences (Sharlip *et al.*, 2002; WHO, 2020) [24]. Male factors alone account for approximately twenty percent of infertility cases and contribute to an additional 30-40% of cases in combination with female factors (Thonneau *et al.*, 1991) [26]. In African populations, male infertility remains a critical issue, with reports indicating sperm-related abnormalities contributing to a large proportion of infertility cases (Agarwal *et al.*, 2015; Uadia *et al.*, 2015) [1, 27]. These concerns underscore the importance of understanding how widely used medications may affect male reproductive health. Ciprofloxacin, a broad-spectrum antimicrobial agent belonging to the fluoroquinolone class, is widely prescribed for urinary tract infections, respiratory diseases, gastrointestinal infections, and several systemic bacterial conditions (Gupta *et al.*, 2011; Mandell *et al.*, 2007) [9, 17]. Although it is approved for use in more than one hundred countries, its safety profile has come under scrutiny due to reports of adverse reproductive outcomes. Experimental findings suggest that ciprofloxacin may induce oxidative stress and

cause structural alterations in testicular tissue, leading to reductions in sperm number and motility, as well as increased morphological abnormalities (Mokhimar *et al.*, 2020) ^[18]. Ciprofloxacin, a broad-spectrum antimicrobial agent belonging to the fluoroquinolone class, is widely prescribed for urinary tract infections, respiratory diseases, gastrointestinal infections, and several systemic bacterial conditions (Gupta *et al.*, 2011; Mandell *et al.*, 2007) ^[9, 17]. Although it is approved for use in more than one hundred countries, its safety profile has come under scrutiny due to reports of adverse reproductive outcomes. Experimental findings suggest that ciprofloxacin may induce oxidative stress and cause structural alterations in testicular tissue, leading to reductions in sperm number and motility, as well as increased morphological abnormalities (Mokhimar *et al.*, 2020) ^[18]. Additional studies have demonstrated that ciprofloxacin exposure may disrupt hormonal homeostasis, including testosterone levels that are essential for normal spermatogenesis (Khan & Sinha, 2012) ^[12]. These observations raise concern about the possible reproductive toxicity of ciprofloxacin, particularly with regard to short-term exposure during active spermatogenic cycles. Despite these findings, most available studies focus on long-term or high-dose exposure, leaving a gap in understanding the acute effects of ciprofloxacin on sperm profiles and testicular structure. Short-term exposure is clinically relevant, as ciprofloxacin is commonly prescribed in brief therapeutic regimens, yet its potential immediate impact on male fertility remains insufficiently characterized.

Therefore, the present study aimed to investigate the short-term effects of ciprofloxacin administration on sperm concentration, sperm quality parameters, and testicular histomorphology in adult male *Wistar rats*.

Materials and Methods

Animal Care

Fifteen adult male *Wistar rats* (*Rattus norvegicus* Berkenhout, 1769) ^[5] were used for this study, with an average body weight of 127 g. The rats were obtained from a reputable breeder in Yenagoa, Bayelsa state, Nigeria. The rats were acclimatized for two weeks and housed in cages under good ventilation and illumination conditions at room temperature ($24^{\circ}\text{C} \pm 2^{\circ}\text{C}$), humidity (68%), under a 12-hour light-dark cycle during the period of the experiment and provided with access to water and a good diet. Care and experimentation were conducted according to the National Research Council guidelines (USA) for the care and use of laboratory animals (National Research Council, 2020) ^[20].

Experimental Design

The rats were randomly divided into three groups of five animals each. Group I served as the control and received distilled water (1 mL). Group II received the low dose, which was administered 22.15 mg/kg body weight per day of ciprofloxacin dissolved in 75 mL of distilled water. Group III (high-dose group) received ciprofloxacin at 44.3 mg/kg body weight per day. The solution was prepared by dissolving ciprofloxacin in 75 mL of distilled water. Treatments were administered orally for four consecutive days. The dose was derived using the body surface area

normalization method, based on a human equivalent dose of 500 mg/70 kg, multiplied by the conversion factor of 6.2 for rats (Reagan-Shaw *et al.*, 2008) ^[22].

Sample Collection and Sacrifice Procedure

Rats were sacrificed by chloroform inhalation, followed by bilateral orchietomy (National Research Council, 2010) ^[19]. The caudal epididymis was dissected and lacerated to release spermatozoa, following established protocols (Salawu *et al.* 2019; Jahan *et al.* 2021) ^[10, 23].

Sperm Motility Evaluation

Fresh semen was expressed onto a pre-warmed microscope slide (27°C) and mixed with two drops of pre-warmed 2.9% sodium citrate. The preparation was covered with a warm coverslip and examined under $\times 400$ magnification. Ten microscopic fields were selected randomly and 100 sperm cells (10 per field) were evaluated. Sperm were classified as motile, sluggish or immotile. Motility percentage was calculated according to WHO criteria (WHO, 2021) ^[29] and methodologies applied in rodent studies.

Sperm Viability Test

Sperm viability was determined using the Eosin/Nigrosin staining method. Two drops of warm stain were mixed with semen on a pre-warmed slide, smeared, and air-dried. Under $\times 400$ magnification, viable sperm excluded stain and appeared unstained, while dead sperm absorbed the dye. Viability percentage was calculated based on the proportion of unstained spermatozoa (WHO, 2021) ^[29].

Sperm Morphology Evaluation

Morphological assessment was performed by mixing semen with Walls and Ewas stain. Air-dried smears were examined under $\times 400$ magnification. Sperm abnormalities involving the head, midpiece, tail and presence of cytoplasmic droplets were counted across randomly selected fields and expressed as a percentage of total sperm observed.

Sperm Count Determination

The right caudal epididymis was dissected, blotted dry and immersed in 5 mL formalin-saline in a graduated test tube. The displaced volume was recorded. The tissue was then homogenized thoroughly, and a portion of the homogenate was loaded into a Neubauer haemocytometer. Total sperm concentration was determined using standard counting protocols widely used in rodent reproductive studies (Cardoso *et al.*, 2023) ^[6].

Histological Processing of Testicular Tissue

Testes were fixed immediately in Bouin's solution for 12 hours and rinsed thoroughly with 70% ethanol. Tissues were dehydrated through ascending grades of ethanol, cleared in xylene, embedded in paraffin, sectioned at $5\text{ }\mu\text{m}$, and stained with H&E. Photomicrographs were obtained at $\times 400$ magnification.

Statistical Analysis

All data were expressed as mean $\pm$ standard error of the mean (SEM). Differences among groups were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's HSD Test for post-hoc comparison. A p-value < 0.05 was considered statistically significant.

Results

Sperm Concentration

Table 1: Mean sperm concentration ($\times 10^6$ cells/mL $\pm$ S.E.M.) in Wistar rats following ciprofloxacin administration

Groups	Mean Sperm Concentration ($\times 10^6$)
Control (distilled water)	40.00 ± 4.18^a
Low dose (22.15 mg/kg)	50.40 ± 2.30^b
High dose (44.3 mg/kg)	65.40 ± 4.63^c

Values with different superscript letters are significantly different at $p < 0.05$ (Tukey's HSD).

Sperm Morphology

Table 2: Mean percentage ($\pm$ S.E.M.) of morphological sperm defects in Wistar rats treated with ciprofloxacin.

Groups	Defect Type	Head (%)	Neck (%)	Tail (%)	Cytoplasmic droplets (%)
Control (%)		27.17 ± 1.53^a	24.25 ± 1.99^a	25.90 ± 1.89^a	21.08 ± 0.92^a
Low dose(22.15 mg/kg)		30.41 ± 1.22^a	25.11 ± 0.76^a	20.02 ± 0.22^b	23.90 ± 1.37^a
High dose(44.3 mg/kg)		29.95 ± 1.38^a	21.43 ± 1.36^a	18.95 ± 0.69^b	12.12 ± 0.36^b

Different superscript letters within the same column indicate statistically significant differences ($p < 0.05$, Tukey's HSD).

Sperm Motility

Table 3: Effect of ciprofloxacin on WHO sperm motility grades (Mean % $\pm$ S.E.M.) in Wistar rats.

Groups	Motility Grade	Grade A (Rapid Progressive)	Grade B (Slow Progressive)	Grade C (Non-Progressive)	Grade D (Immotile)
Control (%)		56.0 ± 2.0^a	14.0 ± 1.0^a	23.0 ± 1.2^a	7.0 ± 0.8^a
22.15mg/kg		52.0 ± 1.5^b	25.0 ± 1.4^b	14.0 ± 1.1^b	9.0 ± 0.9^a
44.3 mg/kg		48.0 ± 1.8^c	28.0 ± 1.7^b	15.0 ± 1.3^b	9.0 ± 1.0^a

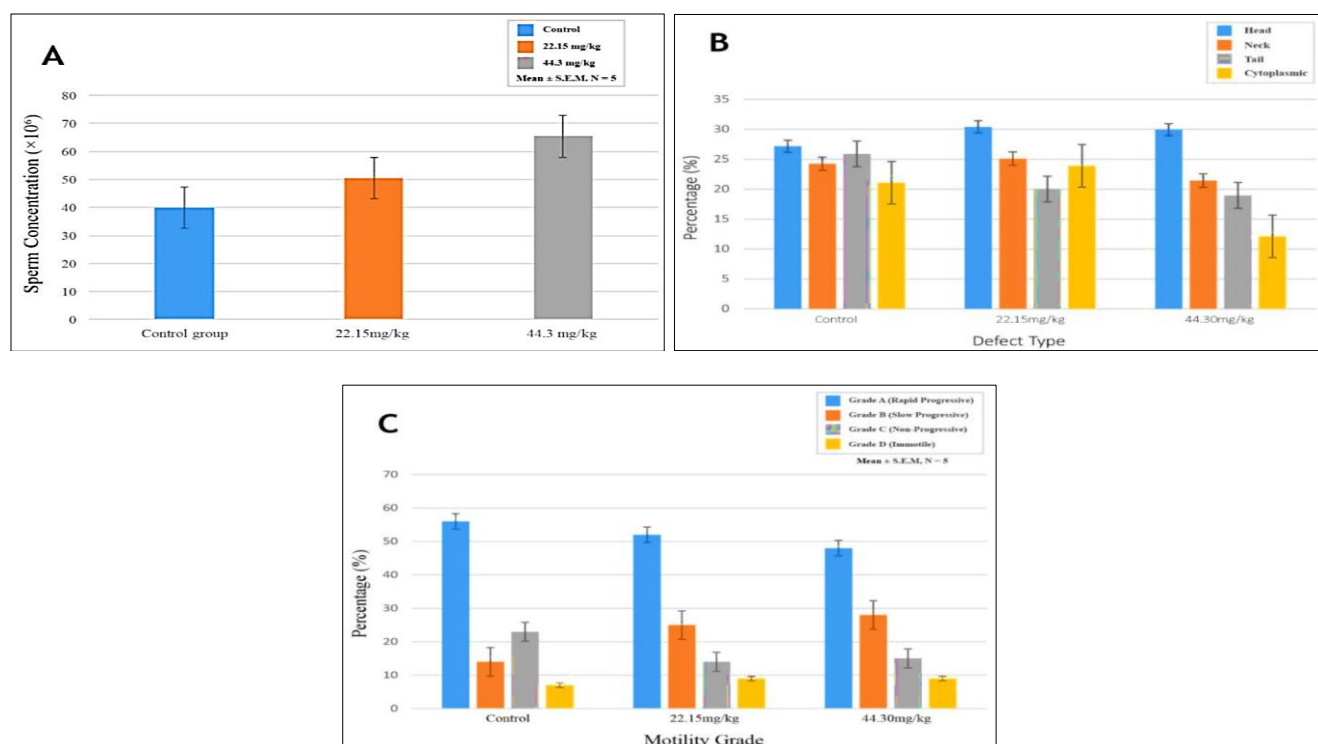


Fig 1: The effect of Ciprofloxacin on sperm parameters in Adult Male Wistar rats (A) Sperm concentration ($\times 10^6$ / mL) : Mean sperm concentration ($\times 10^6$) across the control, 22.15 mg/kg, and 44.3 mg/kg treatment groups. Values are expressed as Mean $\pm$ S.E.M (n = 5). (B) Sperm morphology: Percentage distribution of sperm defects (head, neck, tail, and cytoplasmic droplets) in the three experimental groups. Values are expressed as Mean $\pm$ S.E.M (n = 5). (C) Sperm motility: Percentage of spermatozoa in motility grades A (rapid progressive), B (slow progressive), C (non-progressive), and D (immotile) for each treatment group. Values are expressed as Mean $\pm$ S.E.M (n = 5) (right).

Histological outcomes

Control seminiferous tubules appeared normal, while treated groups showed increasing degrees of spermatogonial hypertrophy, disrupted germ cell layering, and vascular congestion (Figure 2).

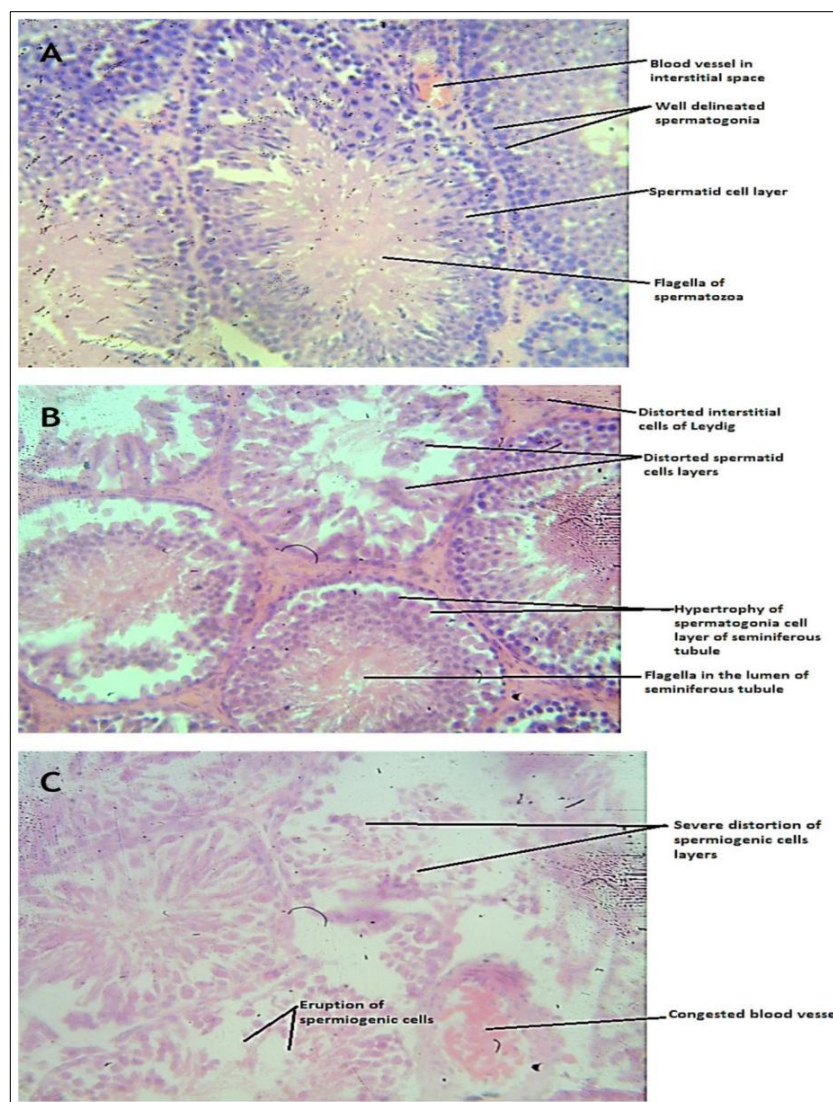


Fig 2: Testicular histology (H&E ×400) (A) Normal seminiferous tubule. (B) Hypertrophied spermatogonia and distorted spermatid layers (low dose). (C) Marked architectural distortion and vascular congestion (high dose).

Discussion

The results from this study provide important insights into the effects of ciprofloxacin administration on sperm parameters and testicular histology in adult male *Wistar rats*. Contrary to the initial hypothesis that ciprofloxacin might reduce sperm concentration and quality due to its potential toxicity, a dose-dependent increase in sperm concentration was observed, from 40.0×10^6 cells/ml in the control group to 65.40×10^6 / ml in the high-dose group, suggesting a potential stimulatory effect on spermatogenesis. This finding contrasts with several reports of adverse effects. For example, Abd-Allah *et al.* (2013) administered ciprofloxacin at a dose of 12.5 mg/kg twice daily for 14 days and reported significant reductions in sperm count and motility, indicating gonadotoxicity. Similarly, Khaki *et al.* (2011) [13] treated rats with 10 mg/kg/day of ciprofloxacin for 60 days and observed decreased sperm concentration and motility. These discrepancies may partly be explained by differences in treatment duration and administration frequency; in the present study, ciprofloxacin was administered once daily over a shorter period. Moreover, species-specific differences and potential adaptive physiological responses to different dosing regimens may account for the contrasting outcomes. Importantly, other studies support the possibility of dose- or

time-dependent hormetic effects of antibiotics on the reproductive system. For instance, Ahmad *et al.* (2014) [2] reported that low doses of ciprofloxacin did not significantly impair testicular function in rats, and even showed mild improvements in some sperm parameters. This aligns with the dose-dependent enhancement of sperm concentration observed in the current study. Sperm morphology analysis provided further evidence of ciprofloxacin's nuanced effects on sperm structure. As presented in Table 2, the reductions in tail and cytoplasmic defects suggest potential compensatory mechanisms at higher doses, possibly promoting structural repair or reducing oxidative stress. A study by Farombi *et al.* (2008) [7] similarly observed reduced abnormalities in sperm morphology following antioxidant co-administration with an antibiotic, indicating that some interventions, or specific conditions, may mitigate damage. In contrast, Zobeiri *et al.* (2013) [30] reported increased sperm DNA damage in rodents treated with ciprofloxacin (12.5 mg/kg twice daily for 14 days), indicating spermatotoxic effects. Again, the higher administration frequency and possible cumulative toxicity in that study differ from the current protocol, where ciprofloxacin was given once daily, allowing more recovery time. Sperm motility, evaluated using WHO-defined categories, also demonstrated dose-responsive trends (Table 3). These

results suggest a shift from rapid to slower motility types with increasing dosage, potentially reflecting altered energy metabolism or structural adaptation in the spermatozoa. However, the absence of a rise in immotility indicates that motility was not fully impaired. Supporting this, Ahmad *et al.* (2014) ^[2] found that short-term ciprofloxacin administration did not significantly impact sperm motility, reinforcing the notion that dose and duration critically influence the drug's reproductive effects.

Histological examination revealed ciprofloxacin-induced alterations in testicular architecture, including spermatogonial hypertrophy, disruption of spermatid layers, and vascular congestion. These findings suggest a degree of testicular toxicity. Supporting evidence comes from Kheirandish *et al.* (2020) ^[14], who observed degenerative changes in the seminiferous tubules of rats treated with 20 mg/kg/day ciprofloxacin for 60 days. Similarly, Abd-Allah *et al.* (2013) reported histochemical disruptions following repeated dosing. While these findings align with the structural changes observed in this study, the extent of damage may differ due to variations in dose, duration, and species.

In conclusion, this study demonstrates that short-term ciprofloxacin administration produces a dose-dependent increase in sperm concentration and improvements in selected morphological parameters in adult male *Wistar rats*. Although motility patterns shifted from rapid to slow progressive movement, overall sperm function was maintained. Histological alterations, including hypertrophied spermatogonia and disrupted seminiferous architecture, indicate underlying testicular stress despite these functional enhancements. These findings challenge the presumed spermatotoxic profile of ciprofloxacin and provide experimental evidence that its reproductive effects are more complex than previously assumed, underscoring the need for further mechanistic investigation.

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