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Contents

Foreword

Greetings to all readers of the Annals of Innovation in Medicine,

As we commence the latest issue of the Annals for the year 2024, it is my privilege to introduce this compilation of groundbreaking research and transformative ideas in the field of medicine.

In a world where medical science is advancing at an unprecedented pace, the need for innovation in healthcare has never been more pressing. The Annals of Innovation in Medicine serves as a platform for disseminating cutting-edge discoveries, pioneering technologies, and visionary approaches that are shaping the future of healthcare delivery and patient outcomes.

Within these pages, you will find a diverse array of articles spanning a wide range of medical disciplines, each offering unique perspectives and insights into the challenges and opportunities facing modern medicine. From groundbreaking research studies to innovative clinical interventions, the articles in this volume represent the collective efforts of researchers, clinicians, and healthcare professionals dedicated to advancing the frontiers of medical knowledge and practice.

As editors, we extend our heartfelt appreciation to the authors for their invaluable contributions and to the reviewers for their diligent evaluation, which have ensured the quality and relevance of the published work.

To our esteemed readers, we invite you to explore the pages of the Annals with curiosity and an open mind. May the discoveries and insights contained herein inspire new ideas, foster collaboration, and ultimately lead to improved patient care and outcomes.

With warm regards,

Nataliya Bhinder
Editor-in-Chief
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Research Article

Serum Levels of Prostate Specific Antigen and Specific Reproductive Hormones Among Male Subjects with Benign Prostate Hyperplasia in Port Harcourt, Nigeria

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Abstract:

Benign prostate hyperplasia (BPH) is a medical condition in elderly men in which there is proliferation and enlargement of the prostate gland. This study evaluated the levels of male reproductive hormones among subjects with BPH. The study involved 150 subjects aged 40 years and above, comprising 80 BPH subjects attending the urology clinic and 70 control subjects. Five millilitres (5ml) of venous blood were collected from each subject into plain bottles for the determination of prostate-specific antigen (PSA), testosterone, prolactin, and estradiol, using the ELISA technique. The mean values of PSA (16.68±10.96 ng/ml), estradiol (71.03±18.56 pg/ml) and for the BPH subjects and prolactin (9.38±4.51 ng/ml) were significantly higher compared to the mean values of PSA (0.48±0.25ng/ml), estradiol (51.33±7.13npg/ml) and prolactin (6.92±1.93ng/ml) of the control subjects. However, the mean testosterone value of the BPH subjects (5.02±1.93 ng/ml) was significantly lower than the mean value for the control (6.57±3.48ng/ml). The BPH who used to consume alcohol had higher PSA (24.26±8.33ng/ml) and testosterone (7.68±3.41ng/ml) compared to the PSA (16.34±3.22ng/ml) and testosterone (4.95±3.62ng/ml) of those who never consumed alcohol. The BPH had significantly altered hormone parameters as well as raised PSA levels. Including hormonal parameters in diagnosing and managing BPH could be an important consideration in our population.

Keywords: Prostate-specific antigen, hormones, prolactin, Benign prostate hyperplasia, testosterone, Port Harcourt, Nigeria

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1. Introduction

Benign Prostate Hyperplasia (BPH) is a medical condition that is characterized by the proliferation and enlargement of the tissues of the prostate gland and is commonly associated with elderly men (1). The symptoms associated with the condition include urinary reluctance, frequent urination, weak stream, and nocturia (2).

The human prostate is made up of both glandular and fibromuscular tissues and has three histological zones, namely the central zone and the peripheral zone (3). The peripheral zone is where prostate cancer primarily occurs, while the transition zone is where virtually all clinically significant BPH develops in the transition zone of the prostate (4). Clinical BPH develops when the hyperplasia of the epithelial tissue and stromal tissues coalesce to form microscopic and macroscopic nodules in the prostate gland. As age increases, every man will eventually develop microscopic nodules under normal physiological function. However, not every man will develop the macroscopic nodules (3). It is the macroscopic growth of the

transition zone that potentially causes the narrowing of the urethra as it passes through the prostate, eventually leading to a bladder outlet obstruction (BOO), which affects urine flow.

Within the transitional zone of the prostate, the proliferation of both epithelial and stromal cells occurs (5). Due to this accumulation of cells in the prostate, prostatitis and fibrosis could develop, which eventually lead to lower urinary tract symptoms (6). It has been established that age is the principal factor for the development of BPH. However, it has also been suggested that androgens can also lead to the condition, in addition to age; androgens are needed for the normal physiological functions of the prostate, but the exact role of androgens in BPH is not clearly understood (7).

The pathogenesis of BPH is yet to be clearly understood (2). However, it is associated with increases in dihydrotestosterone (DHT) levels, which is synthesized from testosterone by the 5α-reductase enzyme within the prostate glands (7). The increased accumulation of DHT in the prostate with ageing leads to an increase in cell growth and hyperplasia (6) because the DHT has a greater effect on the prostate cells than testosterone, principally due to the increased affinity of DHT to the androgen receptors (AR) in the prostate tissue (7).

Generally, BPH can be seen as a result of an imbalance between the homeostatic processes of cell proliferation and cell death, which occur in the epithelial and stromal environments of the prostate. This homeostatic imbalance results in favour of the proliferation of the cells, thereby leading to BPH (8).

Oestrogens have also been associated with the development of BPH; Oestrogens act in ways similar to androgens but do so via different nuclear hormone receptors (Oestrogen receptor alpha- Erα and oestrogen receptor beta- Erβ). Further, testosterone testosterone can be converted to oestrogen by the enzyme aromatase (9).

It appears that the regulation of BPH by the hormones depends on both the androgen receptors and oestrogen receptors in the prostatic tissues (10). Given this, scientific research into the roles of the hormones and their receptors becomes necessary.

Prolactin is produced by prostate epithelial cells under normal physiological conditions in humans (11). It has been proposed that prolactin plays an important role in the development of the prostate gland and simultaneously inhibits apoptosis of the prostatic cells (12). It is reported that prolactin locally produced by the prostate cells can greatly affect the prostate epithelial compartment, resulting in the expansion of the basal and stem-like epithelial cells and marked proliferation of the epithelial cell (11). While some studies have implicated prolactin as a possible contributor to prostate cancer (12), its role in BPH is not clearly understood.

This study seeks to evaluate the levels of testosterone, oestrogen, prolactin and prostate-specific antigen in subjects with BPH.

2. Materials and Methods

I. Study Population

The study involved 150 male subjects, who were 40 years and above, comprising 80 male subjects with benign prostate hyperplasia and attending a clinic at the Rivers State University Teaching Hospital, Port Harcourt, and another 70 apparently healthy male subjects within the same age bracket who served as control subjects.

The sample size for this study was determined using G*Power 3.1.9.2, at a power of 0.8, alpha error probability of 0.05 and effect size of 0.5. The calculated sample size was 64 BPH subjects and 64 control subjects. However, this study adopted 80 male subjects with BPH and 70 male, apparently healthy control subjects.

The ethical approval for this study was obtained from the Rivers State Health Research Ethics Committee. Subjects who participated in this study also gave their oral informed consent to participate in this study.

II. *Eligibility Criteria*

i. Inclusion Criteria: Male subjects, who were 40 years and older, had been diagnosed with BPH (but did not have diabetes, infection of any kind or fertility therapy) and attended clinic at the time of this study. They also consented to participate in this study.

ii. Exclusion Criteria: Male subjects who were less than 40 years old, were on fertility therapy, or had any infection were excluded from this study.

III. *Sample Collection and Analysis*

For this study, 5 ml of venous blood was collected from each subject and put into plain bottles. The samples were spun at 3000rpm, and the serum was collected into another set of plain bottles and stored at -20^{o}C prior to analysis.

Samples were analyzed for prostate-specific antigen (PSA), prolactin, estrogen and testosterone using the ELISA technique for each.

IV. *Data Analysis*

The data from this study were analyzed using SPSS version 23. Results were expressed as mean ± standard deviation. Comparison of means was done using an independent t-test and one-way ANOVA, with p≤005 being considered statistically significant.

3. Results

I. *Comparison of Parameters among Subjects*

The BPH subjects had significantly raised prostate-specific antigen (PSA), estrogen, prolactin, estrogen/testosterone ratio and prolactin/testosterone ratio, but significantly lower testosterone compared to the control subjects.

Table 3.1: Comparison of Parameters among Subjects

	PSA (ng/ml)	**Testo (ng/ml)**	**Estro (pg/ml)**	**PRL (ng/ml)**	**ETR**	**PRT**
BPH Subjects	16.68±10.96	5.02±1.93	71.03±18.56	9.38±4.51	0.021±0.010	2.20 ±0.46
Control Subjects	0.48±0.25	6.57±3.48	51.33±7.13	6.92±1.93	0.011±0.007	1.44 ± 0.51
p-value	<0.001	0.006	<0.001	0.002	<0.001	0.013
t-value	10.444	2.837	6.148	3.195	1.348	1.608

Keys: BPH-benign prostate hyperplasia, PSA-Prostate specific antigen, Testo-testosterone, Estro-estradiol, PRL-prolactin, ETR-estrogen testosterone ratio, PRT- prolactin testosterone ratio

II. *Comparison of Parameters Based on Hypertension*

There were no significant differences in the mean values of estradiol, testosterone, prolactin and PSA between the BPH subjects who had hypertension and those who did not have hypertension.

Table 3.2: Comparison of Parameters Based on Hypertension

	Estradiol (pg/ml)	**Testosterone (ng/ml)**	**PSA (ng/ml)**	**Prolactin (ng/ml)**
Hypertensive	63.71±20.63	6.22±3.54	19.25±12.65	10.50±5.77
Non-hypertensive	65.88±16.08	6.86±4.16	17.50±10.84	10.02 ±4.26
p-value	0.639	0.669	0.395	0.791
t-value	0.475	0.435	0.866	0.268

PSA-Prostate Specific Antigen

III. Comparison of Parameters Based on Alcohol Intake

The BPH subjects who consumed alcohol had significantly raised testosterone and PSA compared to those who did not. There were no significant differences in the mean values of estrogen and prolactin between the BPH subjects who consumed alcohol and those who did not consume alcohol.

Table 3.3: Comparison of Parameters Based on History of Alcohol Intake

	Estradiol (pg/ml)	**Testosterone (ng/ml)**	**PSA (ng/ml)**	**Prolactin (ng/ml)**
No Alcohol	64.82±19.37	4.95±3.62	16.34±3.22	10.85 ±4.71
Alcohol	64.84±17.13	7.68±3.41	24.26±8.33	9.7 ± 5.88
p-value	0.998	0.041	0.007	0.596
t-value	0.003	2.145	1.984	2.598

PSA-Prostate Specific Antigen

IV. Comparison of Parameters Based on Area of Residence

The were no significant differences in the mean values of estrogen, testosterone, prolactin and PSA between the BPH subjects based on whether they lived in urban or rural settings.

Table 3.4: Comparison of Parameters Based on Area of Residence

	Estradiol (pg/ml)	Testosterone (ng/ml)	PSA (ng/ml)	Prolactin (ng/ml)
Rural	65.67±22.39	6.42±3.37	22.46±7.31	6.46±3.37
Urban	64.30±17.01	6.46±4.01	20.31±14.14	6.46 ±4.01
p-value	0.858	0.976	0.293	0.976
t-value	0.181	0.030	1.071	0.300

PSA-Prostate Specific Antigen

V. Comparison of Parameters Based on Previous Urinary Tract Infections

The were no significant differences in the mean values of estrogen, testosterone, prolactin and PSA between the BPH subjects based on their history of previous urinary tract infections.

Table 3.5: Comparison of Parameters Based on Previous Urinary Tract Infections

	Estradiol (pg/ml)	Testosterone (ng/ml)	PSA (ng/ml)	Prolactin (ng/ml)
Previous UTI	66.79±20.71	6.68±3.83	21.08±12.52	9.50 ±4.35
No previous UTI	69.68±15.27	6.09±3.66	18.07±11.38	11.64 ±6.35
p-value	0.235	0.671	0.496	0.318
t-value	1.265	0.431	0.691	1.029

PSA-Prostate Specific Antigen, UTI- urinary tract infections

VI. Comparison of Parameters Based on Body Mass Index (BMI)

There were significant differences in estrogen and PSA levels among the different BMI classifications. However, there were no significant differences in the mean values of testosterone and prolactin.

Table 3.6: Comparison of Parameters Based on Body Mass Index (BMI)

Body mass index (kg/m²)	Estradiol (pg/ml)	Testosterone (ng/ml)	PSA (ng/ml)	Prolactin (ng/ml)
18.5-24.5	67.33±19.52[a]	6.29±5.81[a]	19.14±7.79[a]	10.70±5.83
25-29.5	57.44±16.76[b]	6.93±3.07[a]	17.92±4.69[b]	9.19±1.14
30 & above	44.72±28.90[c]	5.29±1.37[b]	16.17±3.64[c]	10.99±4.69
p-value	0.005	0.638	0.025	0.617
f-value	3.316	3.885	3.806	3.340

Values with different superscripts are significantly different from each other.

Key: PSA-Prostate Specific Antigen

4. Discussion

This study evaluated prostate-specific antigen (PSA), testosterone, estrogen and prolactin in male subjects with benign prostate hyperplasia (BPH). The BPH subjects had significantly raised mean values of PSA, estradiol, and prolactin but significantly reduced testosterone compared to the control subjects. The raised levels of PSA in the BPH subjects could be attributed to the inflammation in the system. Inflammation is one of the key factors in BPH (13). Although the exact mechanism of how inflammation increases PSA levels is clearly understood, it is hypothesized that inflammation causes injury to the epithelium of the prostate, leading to the release of PSA into circulation (14). It has also been reported that men with larger prostate size (such as seen in BPH) produce higher levels of PSA (15). This finding agrees with an earlier work (16).

The testosterone levels were significantly reduced in the BPH subjects compared to the control subjects. This finding agrees with the work of another researcher (17)(16). Testosterone decreases with increasing age (18), with men in their 20s having higher testosterone levels than those in their 30s, 40s, and so on. Thus, the low level of testosterone seen in the subjects in this study could be due to age. It is also known that testosterone can be converted to estrogen by the action of the enzyme aromatase, and this accounts for a large amount of circulating estrogen (19). Testosterone is also converted to dihydrotestosterone by the enzyme 5α reductase (20). These two processes may be responsible for the decreased testosterone in the BPH subjects.

The results from this study also showed that the BPH subjects had significantly raised estradiol and significantly reduced testosterone compared to the control subjects. These findings are in agreement with an earlier study (21). The significantly raised level of estradiol in the BPH subjects may be due to the conversion of testosterone to estradiol. This is probably because, in older men, about 80% of the estradiol is almost exclusively synthesized via the aromatization of testosterone (17). The testes also synthesize some amount (about 20%) of estradiol (19). These processes may explain the high estradiol levels in BPH subjects.

The BPH subjects had significantly higher levels of prolactin compared to the control subjects. This is probably because the levels of prolactin increase with increasing age (22). Also, estrogen stimulates the pituitary gland to release prolactin, which in turn stimulates prostate enlargement (3). However, the exact mechanism of how this effect of prolactin on the prostate occurs in BPH is still under study (23).

The BPH subjects in this study also had significantly higher estrogen-to-testosterone ratio as well as prolactin-to-testosterone ratio compared to the control subjects. The decrease in testosterone and an increase in estrogen in BPH brings about an imbalance between the two hormones, which shifts towards estrogen dominance, as seen in the increased ETR. This increased estrogenic stimulation in the prostate can lead to hyperplasia (24). A similar observation is found with the prolactin-to-testosterone ratio, indicating a raised prolactin level in BPH subjects, probably arising from the stimulation of the pituitary gland by estrogen and local synthesis of prolactin in the prostatic cells.

The hormone parameters did not differ significantly between the BPH subjects who had hypertension and those who did not. This may imply that hypertension does not affect prostate health. Both hypertension and BPH have some features in common, though they are different disease entities; they are age-related conditions in older men, they involve the sympathetic nervous system and treatment for both involves alpha-adrenergic blockers (25). Our finding here may be because the two conditions do not share the same pathophysiological mechanisms (26). Similarly, this study found no significant differences in the hormone parameters among the BPH subjects based on area of residence (urban/rural) and previous urinary tract infection history.

The BPH subjects who used alcohol had significantly raised PSA levels compared to those who did not drink alcohol. A previous study had earlier reported a similar finding (27). There was also a significantly raised testosterone in the BPH who used alcohol compared to those who did not. A previous study in China (28) had reported a similar finding. However, another study (29) reported that there is an association between modest alcohol intake and decreased benign prostatic hyperplasia diagnosis. It is, therefore, possible that the effect of alcohol on BPH could be dose-dependent, with moderate intake giving beneficial effects. The raised testosterone in this study is probably because alcohol acts as a hormone disruptor in males (28).

Results from this study showed that, among the BPH subjects, the estradiol, testosterone and PSA decreased significantly with increasing body mass index (BMI). This finding has been reported by an earlier study (30). Obesity is known to increase the risk of BPH (31). This association between BMI and decreased PSA levels among our subjects may be due to lower testosterone serum levels (32) or probably due to plasma hemodilution because obesity causes larger plasma volume compared to non-obese individuals (33).

5. Conclusion

The data from this study indicate that BPH subjects had significantly raised PSA, estradiol, prolactin, estradiol/testosterone ratio and prolactin/testosterone ratio. However, they had significantly reduced testosterone levels. There were no differences in the hormone parameters among the BPH subjects based on area of residence (urban or rural) and previous history of urinary tract infections or hypertension. However, previous alcohol consumption increased testosterone and PSA levels compared to those who never consumed alcohol. Based on BMI classification, estradiol, testosterone, and PSA levels significantly reduced as BMI increased. Hence, it is important to consider hormone parameters when managing BPH.

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Case Report

Retrocaval Ureter Associate with Ureterolithiasis: Case Report

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Abstract:

The retrocaval ureter is a congenital anomaly in which the ureter passes posteriorly to the inferior vena cava (IVC). This condition is rare and promotes compression of the upper segment of the ureter, leading to urological symptoms, the main one being hydronephrosis.

We present a case of the Hospital Regional do Vale do Paraíba from the year 2022 of retrocaval ureter associated with ureterolithiasis, whose endourological treatment allowed the successful treatment of urinary lithiasis safely despite the congenital anomaly presented by the patient.

Keywords: retrocaval ureter; ureterolithiasis; endourological treatment.

Introduction

The retrocaval ureter is a congenital anomaly that occurs between the 4th and 8th weeks of intrauterine development and is due to the abnormal formation of the infrarenal inferior vena cava (IVC) from the subcardinal vein located anteriorly instead of the supracardinal vein located posteriorly (1). Thus, the ureter passes posteriorly to the inferior vena cava. The prevalence of this anomaly is around 0.13%, predominates in males in relation to females (3:1), and is usually on the right side (2). Therefore, it is a rare condition and its presence should be suspected by doctors, especially in the presence of urological symptoms without a clear cause. These symptoms may manifest mainly by hydronephrosis since IVC compresses the upper segment of the ureter, leading to different degrees of this condition (3).

The association of the retrocaval ureter with calculus in the loop segment of the ureter is extremely rare (4). However, it is a condition of high social impact and high cost, considering that it affects 5% to 15% of individuals at some point in life and also has high recurrence rates (5). It affects the population in a ratio of three men to every woman, especially in the 20-50 age group. Industrialized countries with tropical climates have a higher incidence of kidney stones when compared to developing countries, a fact resulting from the differences between the type of diet and water loss due to sweat (6). In addition, ureterolithiasis consists of the presence of a kidney stone in the ureter, causing symptoms such as severe colic, nausea and vomiting and can lead to hydronephrosis, as well as cause damage to renal function.

The patient in the present clinical case presents a retrocaval ureter associated with ureterolithiasis, whose endourological treatment allowed the successful therapy of urinary lithiasis safely despite the congenital anomaly presented. Since it is a case of rare association, it is highly relevant for discussion.

Case Report

SRM, 51 years old, female, white, born and coming from Pindamonhangaba-SP, with chronic obstructive pulmonary disease, hypertension and depression. She was referred to the

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Urology Department of the Hospital Regional do Vale do Paraíba (HRVP) due to right low back pain two days ago, associated with chills. Blood count and examination of abnormal elements and sediments of the urine were requested, which showed: 17,600 leukocytes per microliter of blood, positive nitrite in the urine and 975,000 leukocytes per field. Computed tomography of the abdomen was also requested, which demonstrated mild right ureteral dilation, pelvic calcifications on the left, which may correspond to phlebolites; on the right there was an image in the ureteral path that raised doubts about whether it was vascular calcification. In view of these results, it was decided to perform abdominal tomography with contrast, in order to obtain a better observation of stones.

The patient was submitted to a new computed tomography of the abdomen with contrast, which showed retrocad ureter, with mild upstream ectasia, which is justified by the anatomical alteration; middle ureter with calcification in its topography, which suggests calcification in the internal iliac artery; presence of free fluid in the pelvis in moderate amount. In view of the above result, it was decided to admit the patient, antibiotic therapy and new laboratory tests were performed. In these tests, the patient had a reduction in the leukocyte count to 8300 cells per microliter of blood.

Thus, the passage of a double J (Figure 1) catheter was performed on the right without wire, the passage of hydrophilic guide wire did not present any output of secretion of infectious aspect, however, the performance of ureteroscopy was impossible due to ureteral compliance. The patient evolved without intercurrences and was discharged from the hospital three days after surgery, and returned to the outpatient clinic two days after discharge, complaining of constant pain in the right flank, burning, associated with dysuria. As a result, a new Computed Tomography of the abdomen was performed, which did not show new ureteral stones, so it was decided to remove the double J catheter and the patient was discharged the next day.

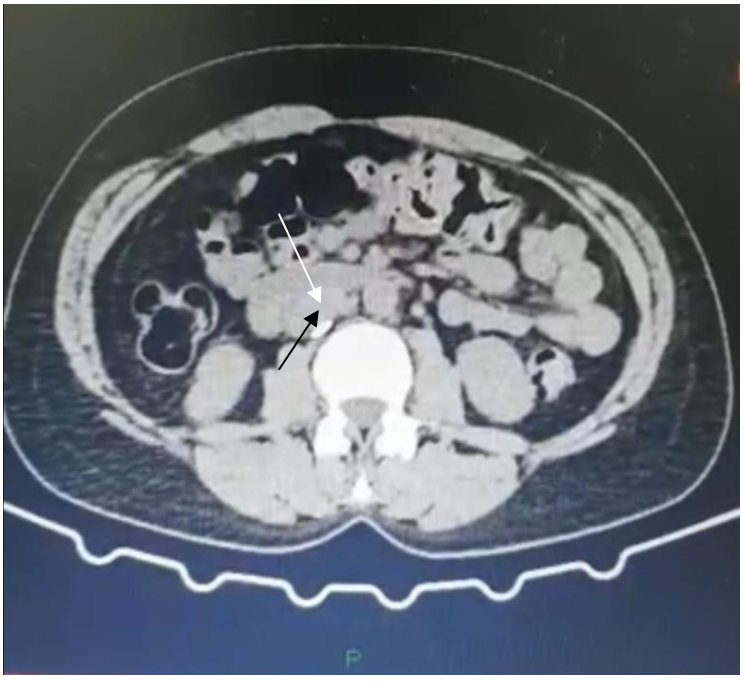

Figure A Tomography of the abdomen in the axial section, showing an anomalous trajectory of the right ureter. Black arrow: right ureter with double J. White arrow: right vena cava.

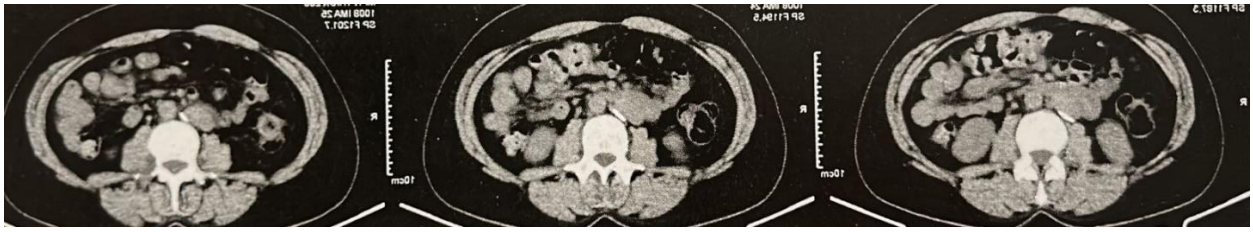

Figure B Tomography of the abdomen in the axial section, showing ureter with catheter passing posteriorly to the vena cava.

Discussion

The retrocava ureter is a rare condition that triggers the entrapment of a proximal segment of the ureter, resulting in the involvement of the ureter around the IVC. Although congenital, it usually becomes symptomatic in the third or fourth decade of life due to hydronephrosis by compression of the IVC-segmented ureter against the psoas muscle, ureteral torsion or an adynamic retrocaval ureteral segment. The main symptoms and complications include abdominal pain, hematuria, urinary tract infection, stone formation, and renal dysfunction[1].

In addition, it may be associated with other anomalies mainly in the urogenital organs and cardiovascular systems. Some of these include IVC duplication, situs inversus, imperforate anus, esophageal atresia, myelomeningocele, renal agenesis, shoe-wearing horse, ureteral duplication, congenital absence of deference vessels, hypospadias, intestinal malrotation, VACTERL, and Turner's branchial arch (7).

In the present clinical case, the patient reported was female and was in the fifth decade of life. She had a picture of right low back pain associated with chills, which made her seek the health service. During the investigation of the clinical picture, a urinary tract infection, ureterolithiasis and the presence of retrocava ureter were evidenced, with mild upstream ectasia; middle ureter with calcification in its topography; presence of free fluid in the pelvis in moderate amount.

In the literature, this condition was classified into two types according to the radiographic appearance and the site of ureteral narrowing. Type I, most commonly, the ureter reveals a typical "hook" shaped deformity, displaying an inverted J or S figure over the site where the obstruction is. The obstruction causes dilation of the proximal upper urinary tract at the level of the lateral face of the IVC. Type II, on the other hand, the post-cava segment of the ureter crosses higher at the level of the renal pelvis.

Treatment is based mainly on clinical presentations, degree of hydronephrosis and existence of impaired renal function. In patients without subjective symptoms and without hydronephrosis, surgical correction is not mandatory, justifying therapeutic abstention[3]. Therefore, due to the symptomatic picture presented by the patient, she was submitted to endourological treatment, obtaining success in the therapy of ureterolithiasis, despite the anomaly.

Conclusion

The retrocava ureter associated with ureterolithiasis is a rare entity. Computed tomography and magnetic resonance imaging are the best tests for investigation and diagnosis. Surgical treatment is recommended in symptomatic cases and usually leads to complete resolution. In the case reported, as the patient was symptomatic, the endourological treatment was resolutive.

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Narrative review

Epidural and Intrathecal Drug Delivery Systems for Chronic Pain Management: Progress, Promises, and Challenges

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Abstract:

Millions of people worldwide suffer from chronic pain, which significantly impacts their quality of life. Managing chronic pain is often complex and time-consuming. In this narrative review, we explore the use of epidural and intrathecal drug delivery systems (EIDDS) as a solution for chronic pain management. The purpose of this review is to provide an overview of recent approaches in targeted implantable drug delivery systems for chronic pain management, including their long-term safety, efficacy, cost-effectiveness, risks, and future opportunities and challenges. The data was gathered through extensive research using MEDLINE, PubMed, and Google Scholar databases, including studies published until June 13, 2023. The visual analogue scale, Karnofsky Performance Status (KPS), respiration, and oxygen saturation in the group receiving drugs through a targeted implantable drug delivery system were significantly better than those in the group receiving conventionally administered analgesia in a study on patients with advanced cancer. Whereas in comparison to conventional treatment alone, the targeted implantable drug delivery system alone or in combination therapy exhibited some advantages or similar effects in reducing chronic pain during a 1-year follow-up in patients with chronic non-cancer pain. Implantable drug delivery systems are a promising new treatment option for chronic pain treatment. All forms of pain, including those that are still challenging to treat with traditional methods, can now be targeted with devices and treatments.

Keywords: Chronic pain; Intrathecal; epidural; implantable drug delivery systems, epidural and intrathecal drug delivery system, EIDDS

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1. Introduction

At least 10% which is around 780 million individuals worldwide suffer from chronic pain, which impacts a sizable section of the population. The prevalence increases up to 25% of people who live in developing nations, are suffering from chronic pain (1).

Up to 85% of people with chronic pain report having severe depression, which is a startling statistic that highlights the impact this ongoing physical struggle has on mental health (2). Even more concerning, there is a strong correlation between chronic pain and suicide risk. Research indicates an alarming increase in suicides associated with chronic pain, accounting for 10.2% of suicides in 2014. Notably, opioid overdose accounted for 16.2% of suicides involving chronic pain, underscoring the possibility of opioid usage as a coping method (3). The detrimental impacts go beyond the body. Patients with chronic pain commonly struggle with sleep disturbances, with nearly half of them reporting a substantial sleep deficit of 42 minutes each night. Their physical and mental health continue to deteriorate as a result of this

poor sleep, starting a vicious cycle. (4). Long-term effects of chronic pain on quality of life are evident, as it raises the risk of depression, suicide, opiate use, and sleep disturbance. It's a complicated problem that needs to be addressed in order to enhance the general health of millions of people worldwide (5).

Conventional treatments for chronic pain, such as Oral Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), opioids, antidepressants, antiseizure medications, and anxiolytics, can be effective for some patients. However, occasionally, they are less effective and have specific drawbacks (6). Due to the fact that chronic pain is a complex condition with a variety of underlying causes and that people respond differently to different treatments, one of the limitations of conventional treatments is their effectiveness. While these therapies can relieve pain for some patients, they may not work equally well for everyone. These types of treatments not only have variable efficacy but also frequently cause adverse consequences. For example, stomach ulcers and bleeding are gastrointestinal problems that can be brought on by oral NSAIDs. Opioids have a high risk of addiction, tolerance, and dependence, even though they are frequently recommended for severe pain. For instance, the opioid crisis in the US has brought attention to the possible risks associated with long-term opioid usage. While thinking about opioid medication for the treatment of chronic pain, it is important to carefully consider the advantages and disadvantages (7).

Furthermore, due to the drawbacks and dangers of conventional medicines, alternative therapeutic modalities are required. For example, targeted implanted drug delivery systems enable the localized distribution of analgesic drugs to the site of pain, which may minimize systemic adverse effects. Other treatment options, such as physical therapy, cognitive-behavioral therapy, and complementary and alternative medicine, may be more effective for more people who are not responsive to conventional therapies (8, 9).

The epidural and intrathecal drug delivery system (EIDDS) is a medical device that can be surgically inserted inside patient tissues to deliver a therapeutic substance and enhance its effectiveness and safety by managing the rate, timing, and location of drug release in the body (10). The importance of employing EIDDS for managing chronic pain is that they can offer a more reliable and controlled medicine delivery than traditional techniques, including oral tablets or injections. This may lessen pain flare-ups since these devices help overcome treatment compliance or adherence issues associated with conventional drug forms like oral drugs or injectables. Additionally, EIDDS can be designed to give medication at predetermined intervals or in reaction to specific events like changes in body temperature or level of activity (11, 12). Ensuring the patients take the appropriate dosage at the appropriate time can further enhance pain control. However, there are certain knowledge gaps regarding the application of EIDDS for the treatment of chronic pain. For instance, it is not yet known how long EIDDS can be used safely or what these devices' potential long-term negative effects are. In addition, some patients may find the cost of EIDDS to be prohibitive. Some risks may be faced during the treatment of chronic pain through this method, such as infection, drug toxicity, and other complications (13, 14). Therefore, this review will provide an overview of recent targeted implantable drug delivery system treatment approaches available for chronic pain management. Also, its long-term safety, efficacy, cost-effectiveness, risk, and future opportunities and challenges will be covered.

2. Method

According to published guidelines on narrative reviews, a review of studies looking into implantable drug delivery systems as a potential therapy option for managing chronic pain was conducted (10). The published paper to June 13, 2023, was manually searched on MEDLINE PubMed and Google Scholar. Pain, chronic pain, implanted drugs, opioids, epidural, intrathecal, cancer, and non-cancer were used in combination with free-text and MeSH terms. Studies that looked at methods for the treatment of chronic pain were chosen for inclusion. The search was limited to English-language articles only.

3. Neuroanatomy and physiology of the Epidural and Intrathecal Spaces for Targeted Drug Delivery

The dura mater, arachnoid mater, and pia mater protective membranes surround the spinal cord, which is suspended in a medium of cerebrospinal fluid (CSF) (15). The arachnoid mater is tightly adhered to the exterior, robust dura mater, while the pia mater covers the spinal cord. All three membranes are outside of the epidural space. Rich venous plexus, spinal arterioles, lymphatics, and extradural fat are all present in the epidural area. The CSF is located in the intrathecal space between the arachnoid and pia maters (16).

The 31 pairs of spinal nerves, each with an anterior and a posterior root, exit through the foramina between the vertebrae. Each spinal neuron supplies/innervates a particular portion of the skin's surface, known as a dermatome. The epidural space is the area outside the dura mater. Analgesics are injected into the epidural space during epidural analgesia. An indwelling catheter may be used to administer analgesics continuously or as a single injection (17).

The delivery of analgesic medications (such as those mentioned above) directly into the CSF in the intrathecal space is known as intrathecal analgesia. The subarachnoid space is another name for the intrathecal space. Since analgesics administered this way are about ten times more powerful than those administered into the epidural area, lesser doses and volumes may be needed (18).

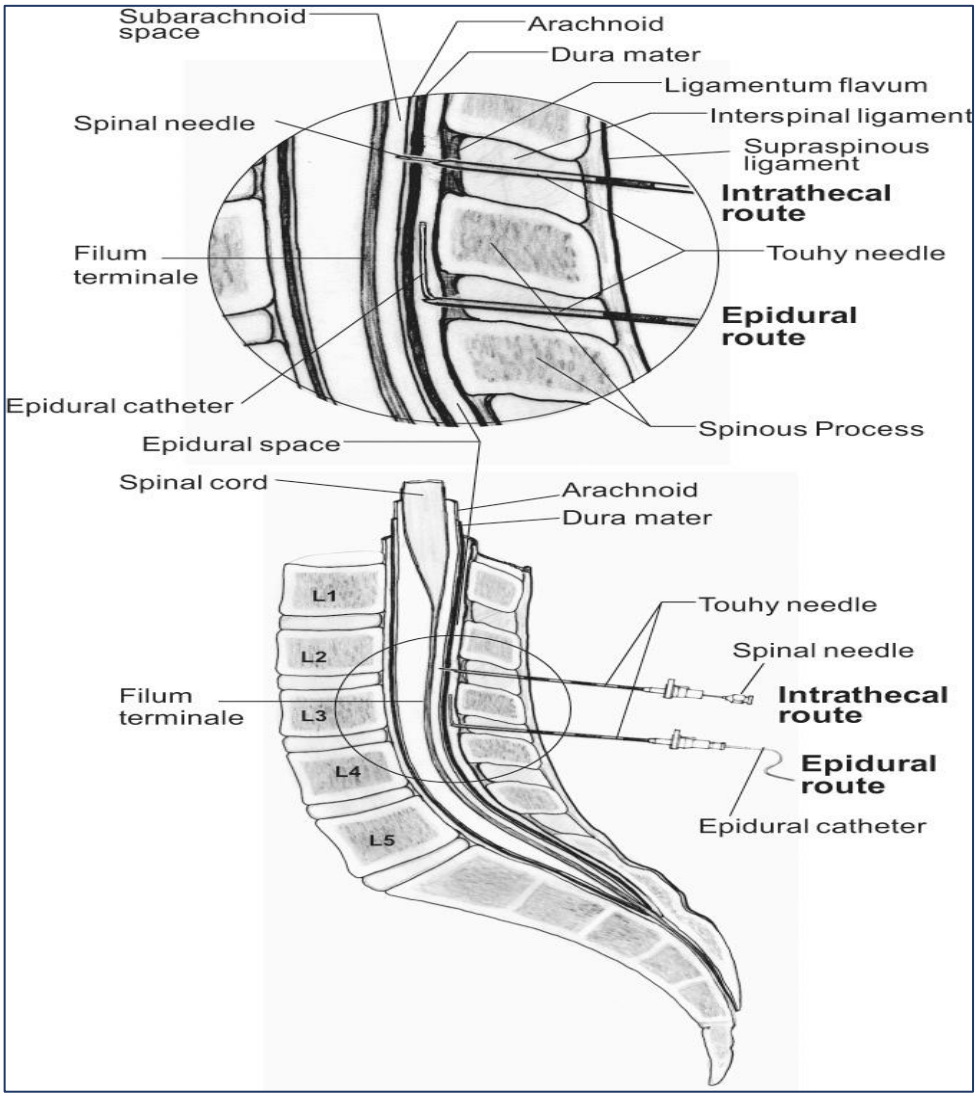

Figure C Gross anatomy of the spinal cord. Cox F (2009), Perioperative Pain Management, Wiley-Blackwell (16).

4. Indications and Patient Selection for EIDDS

Depending on the underlying cause of the pain, chronic pain can be divided into malignant and non-malignant categories. Cancer or another progressive disease is the source of malignant chronic pain, although non-malignant chronic pain can be brought on by several other conditions, including injury, inflammation, or nerve damage (19). Cancer and non-cancer-related pain are further subgroups of indications for the use of intrathecal or epidural medication delivery systems in the treatment of chronic pain. To properly treat cancer-related pain, patients may require substantial dosages of oral opioid medicines that are resistant to traditional medical therapy (20). Patients are vulnerable to systemic side effects of these drugs at such high dosages of oral opioids, which may include constipation, respiratory depression, and even death. Providing appropriate analgesia without causing systemic side effects and enhancing the quality of life may be achieved with intrathecal and epidural administration of opioids (21). Most people who are chosen for this pain treatment that is not cancer-related and typically have spine diseases as the cause of their pain. Compression fractures, spondylolisthesis, spondylosis, failed back surgery syndrome, and spinal stenosis are only a few examples of these diseases (22). Complex regional pain syndrome, pelvic pain, and abdominal pain are some other non-cancer-related pain syndromes that are being addressed by EIDDS since they are typically resistant to other treatment techniques (23).

The following are the standard selection criteria for patients who are qualified for intrathecal medication infusion pump implantation (24, 25):

1) A patient who has failed to respond to conservative treatment and has moderate to severe pain (VAS > 4).

2) A successful trial is generally considered to have a test phase that provides adequate pain control (>50% improvement for at least 10 hours is traditionally considered adequate), with manageable side effects, and 50% functional improvement (Implantable drug delivery for chronic pain management-scope, limitations, and future).

3) The patient's treatment response is subpar, and the usage of oral/transdermal medication causes unacceptably bad adverse effects.

4) The patient has a healthy spinal column that is suitable for the implantation of a spinal infusion system.

5) The patient must give informed consent, and no chronic hematologic problems or active infection would preclude implantation.

6) The patient has no skin conditions and no prior history of pharmacological or common infusion system component allergies.

7) The patient has no history of substance misuse (alcohol or drugs) and no psychiatric or psychological disorders that would rule out implantation.

5. Evidence bases for effectiveness in malignant and chronic non-malignant pain

a) Epidural and intrathecal drug delivery system for the management of chronic pain related to cancer

In 2018, 9.6 million people died from cancer, which is the second largest cause of death worldwide. 2 million individuals worldwide endure pain each day, and cancer pain is one of the most serious unaddressed public health issues (26). More than 70% of cancer patients with advanced illness experience pain. In patients with advanced cancer, the introduction of targeted implantable medication delivery devices significantly reduces systemic opioid consumption.

Recent research indicates that when compared to intravenously delivered analgesia, epidural implanted drug delivery systems had a greater incidence of chronic pain control and enhanced quality of life. The respiration and oxygen saturation in the group receiving epidural self-controlled analgesia (n = 26) were significantly better than those in the group receiving intravenous self-controlled analgesia (n = 24) in a study of 50 patients with advanced cancer. In the group receiving epidural self-controlled analgesia, the visual analog scale (VAS) was significantly lower than in the intravenous self-controlled analgesia group, and the Karnofsky score was significantly higher in the epidural self-controlled analgesia group than in the intravenous self-controlled analgesia group. Patients who received epidural self-controlled analgesia reported higher levels of satisfaction and fewer side effects than those who received intravenous self-controlled analgesia. In patients with advanced cancer, self-controlled epidural analgesia may significantly increase the quality of life and reduce discomfort (27).

From May 2014 to May 2018, Sindt, Jill E., et al. (28) performed a retrospective review of individuals who received EIDDS treatment for cancer pain. There were 173 patients in all, and 93% of them had stage IV illness. The median daily oral morphine equivalent (OME) before the implant was 240 mg (interquartile range: 130-390, range: 0-2616 mg). 57% of patients needed OME doses greater than 200 mg/day, and 19% needed doses greater than 500 mg/day. The interquartile range for the post-implant median OME was 0 mg (range 0-480 mg), and 82.6% of patients fully stopped using systemic opioids. Only 1.7% of patients used more than 200 mg of OME, whereas 11.0% of patients used less than 100 mg. Following EIDDS implantation, the mean OME was reduced by 94% (p 0.0001), and all patients who continued to use systemic opioids needed less OME than they had before the implantation. The authors conclude from their finding that implantation was linked to a considerable decrease in systemic opioid use 30 days after surgery in the largest cohort of patients with advanced cancer and refractory pain treated with EIDDS, with the vast majority of patients quitting systemic opioids. Patients who kept taking systemic opioids had lower levels of pain control than those who are implanted.

When the conventional WHO strategy has failed to adequately treat a patient's cancer pain, intrathecal medication administration is effective. Using the Brief Pain Inventory, Abdelemam, Rania M., et al (29) compared the level of pain relief in 22 patients between 2008 and 2013 before and after the placement of an intrathecal medication delivery system. They noticed a clinically and statistically substantial improvement in their pain right away. The average pain score on the Brief Pain Inventory decreased from 6.8 to 3.0 one week after insertion. Over six months, there was continued improvement in the pain scores. The authors conclude their case study that patients with difficult-to-control cancer pain can benefit from efficient pain treatment for several months with the proper use of intrathecal implantable medication delivery devices.

Intrathecal or epidural medication delivery systems have adequate and better pain management even when cancer has gone to an advanced stage. From 2013 to 2017, Streans, Sita M., et al (30)conducted a prospective, long-term, multicenter cohort study on 1141 cancer patients. According to the patient report, intrathecal implantable drug delivery systems can effectively and efficiently manage cancer patients' pain, even in more advanced stages of the disease, while simultaneously preserving their quality of life. The EuroQol with 5 dimensions (EuroQol-5D) scores within the cohort of patients who provided baseline and follow-up data significantly improved at 6 (P =.0007; n = 103) and 12 (P =.0026; n = 55) months compared to baseline, with significant improvement at 6 months (P =.0016; n = 41). 3.2% of patients had infections that required surgical treatment (IDDS explant, replacement, pocket revision, irrigation and debridement, etc.). According to the authors, this large-scale, multicenter, single-group cohort study adds to the body of previous RCT data that supports EIDDS as a secure and efficient therapeutic option with a favorable benefit-risk balance for the management of cancer pain. But this research was done on a single group of population without comparator and most patients presented were treated at a single center in the United States even if it uses large numbers of patients.

A Wilcoxon Signed-Rank test was used on 160 patients to assess the degree of pain relief, efficacy, and safety of patients who underwent EIDDS implantation at a multidisciplinary pain clinic. The charts of the patient's demographics, cancer type, and pain scores were

reviewed retrospectively. According to this retrospective review study, EIDDS can reduce cancer pain in a range of individuals, and it should be strongly examined as a treatment option for people whose cancer pain is unmanageable with conventional medical treatment(31). At the time of implantation, the median pain score was 7.1, and one month later, it was 5.0. The median reduction in pain was 2.5 for those who had baseline and one-month pain scores available (p 0.0001). Three months after implantation, pain assessments did not significantly change from those at one month. The median lifespan was 65 days. Since this research used a retrospective study design, the majority of the data came from doctor notes, which frequently lacked all of the relevant criteria. Additionally, there were no defined means for gathering chart data, such as pain scores, which could have indicated the patient's current suffering, average pain, or maximal agony. Due to the institution's extensive referral network and the fact that many patients obtained additional care nearby, follow-up statistics were limited. Even if those limitations are present there is insufficient evidence to support additional randomized trials comparing EIDDS to conventional medical management, despite the well-established advantage of EIDDS for the treatment of cancer pain.

Compared to comprehensive medical management alone, another randomized clinical trial using targeted implantable drug delivery systems with comprehensive medical management demonstrated superior clinical outcomes at 4, and 12 weeks for cancer treatment. In comparison to non-IDDS patients, the EIDDS VAS pain scores dropped by 60% at 4 weeks (P = 0.002) as opposed to 37%. In comparison to the non-IDDS group, the IDDS VAS pain scores had declined by 42% after 12 weeks, whereas they had decreased by 47% (P = 0.23). When CMM patients switched over and received EIDDS implants, the most resistant group, they experienced pain VAS reductions of 27%, which were clinically and statistically significant. EIDDS boosted cancer patient survival, increased therapeutic success, decreased pain scores, and alleviated most drug toxicity (21).

Overall, studies have indicated that epidural and intrathecal implantable drug delivery systems provide better pain relief and enhanced quality of life compared to conventional methods. These systems have been found effective even in advanced stages of cancer, with a substantial decrease in systemic opioid use and improved pain management. The use of implantable medication delivery systems, along with comprehensive medical management, has demonstrated superior clinical outcomes, including reduced pain scores and improved therapeutic success. Further research and randomized trials are needed to explore the full potential of these systems and compare them to conventional approaches

b) Epidural and intrathecal drug delivery system for the management of chronic pain related to non-cancer

Pain that generally lasts longer than six months in a patient who does not have cancer is referred to as chronic non-malignant pain. An essential element of interventional methods for refractory chronic pain disorders is implantable medication delivery systems. When compared to systemic opioid administration, continuous intrathecal or epidural opioid injection leads to higher subarachnoid drug concentrations, better pain scores, and fewer adverse effects (32). One international multicenter randomized, double-blind crossover study has shown that for chronic non-cancer patients, intermittent bolus infusion and continuous infusion have nearly comparable pain-controlling abilities, after the patients are implanted with a programmable intrathecal drug delivery (ITDD) device, either of intermittent boluses or a simple continuous flow in period 1, followed by a crossover to the alternative mode of administration, Eldabe, Sam., at al found that there is no significant difference in the Patients' Global Impression of Change (PGIC) scale. The authors came to this conclusion based on their observation that intermittent bolus dosing did not significantly alter the mean PGIC or the proportion of positive responders, and both ways of administration have significantly improved in controlling chronic pain than traditional or conventional ways of administration (33). In another study conducted to treat severe intractable chronic non-malignant pain, Hamza, Meged, et al (34)compared intrathecal boluses to continuous infusion trialing approaches before and after the implantation of drug delivery devices. Throughout the observation period, authors observed a statistically significant decrease in pain and an increase in function in both cohorts after DDS (drug delivery system) implantation. The overall limited dose escalation also applied to the IT dose, which remained almost stable throughout. There

was a considerable decline in oral opioid consumption. Between the two cohorts, there was no statistically significant difference in the prediction of trial success or long-term results. From this prospective, randomized, side-by-side, long-term study the authors conclude that intrathecal opioids with a drug delivery system at low doses can significantly and sustainably reduce pain in patients with chronic non-cancerous pain and improve function (physical and behavioral).

However, other writers, like Hayes et al. (35), challenge the risk/benefit ratio in patients with persistent non-malignant pain due to inconsistencies in the administration of intrathecal medication infusion in these individuals. They discovered that the use of IDDS (intrathecal drug delivery system) was of minor analgesic effect in the first 6 months of therapy, which was reduced over the longer term in their case-control research on 25 patients. They also saw a constant lack of functional improvement throughout IT therapy, a pattern of inactivity concerning self-management, and a considerable reinforcement of the sickness role. Adverse effects and dose escalation were frequently used on these patients. 24 out of 25 patients stopped receiving IT therapy, with 7 (29%) having urgent IDDS-related problems, 16 (67%) transitioning to oral/transdermal administration electively, and 1 due to a death unrelated to IDDS. Reduced physical activity, temporary withdrawal symptoms, and greater pain were all negative effects of stopping the medication. Contrarily, patient-reported benefits following the end of opioid infusion included fewer side effects (sweating, weight gain, and edema), the discontinuation of testosterone replacement therapy in some cases, increased comfort due to the disappearance of the abdominal mass effect brought on by the infusion device, and reduced hospital dependence due to fewer follow-up visits to the pain unit.

There is also another retrospective cohort study that shows that there is no significant difference in opioid consumption between patients who took conventional and implantable delivery systems in 6 months of treatment. From a total of 82 patients, the 12-month average morphine equivalents daily dosages (MEDD, mg/day) was considerably lower in the IDDS group compared to the comprehensive medical management (CMM) group (53.2 46.3 vs 123.9 176.4, respectively; P = 0.008), even though the 6-month average MEDD did not reach statistical significance. At baseline, ER visits were more common in the IDDS group than the CMM group (5.4 vs 0.5, respectively; P =.002), and this difference persisted for 12 months (P 0.001). Other than that, there was no difference between the groups during 12 months in the frequency of hospitalizations and medical costs for pain management. The authors conclude from their findings in comparison to CMM alone, the combination IDDS therapy exhibited some advantages in reducing opioid intake during a 1-year follow-up in patients with chronic non-cancer pain (36).

In general, studies have demonstrated that continuous intrathecal or epidural opioid injection leads to higher drug concentrations, improved pain scores, and fewer adverse effects compared to systemic opioid administration. The use of programmable ITDD devices, whether through intermittent bolus infusion or continuous infusion, has shown comparable pain control abilities. Implantation of drug delivery devices has been associated with a significant decrease in pain, increased function, and reduced oral opioid consumption. However, some researchers challenge the risk/benefit ratio of intrathecal medication infusion, citing inconsistent analgesic effects and limited functional improvement.

c) Epidural versus intrathecal implantable drug delivery system

Patients with neuropathic chronic pain, frequently brought on by spinal cord injury, are the main population for which intrathecal and epidural medication delivery systems are used. These techniques rely on implanting a pump/reservoir in a subcutaneous pocket under radiological guidance (37).

One well-designed trial demonstrates that, in cancer patients undergoing gastrectomy surgery, single-dose epidural opiates are more effective at reducing hospital stays than single-dose intrathecal opiates. The opioid consumption at 12, 24, and 48 h postoperatively was significantly lower in the thoracic epidural analgesia group than in the intrathecal morphine group at all time points, according to Desjardins, Philippe et al.'s (38) analysis of 79 patients who underwent gastrectomy for cancer from 2007 to 2018 over 11 years. At all-time points,

the intrathecal morphine group had a higher pain numeric rating scale score than the thoracic epidural analgesia group did. However, another similar study was carried out between July 2020 and June 2021 on fourteen patients who underwent pancreatoduodenectomy through an upper midline incision for neoplastic or pre-neoplastic illness. They conclude that epidural and intrathecal implanted drug delivery systems' baseline features did not differ statistically significantly from one another (39). However, further study is needed since the available studies on this topic are very limited.

6. Drugs used in epidural and intrathecal drug delivery for chronic pain

Epidural and intrathecal drug delivery (EIDD) aims to reduce the dose and adverse effects of the drugs by bringing them close to the receptors that affect pain modulation (40). The introduction of permanent intrathecal and epidural catheter implantation, along with internal or external ports, reservoirs, and programmable pumps, marked the beginning of intrathecal drug delivery (41).

EIDD is an effective medication for cancer patients with pain that won't go away. Patients with pain unrelated to cancer should only be given the choice of EIDD after exhausting all other treatment alternatives, such as spinal cord stimulation. The United States Food and Drug Delivery has only licensed morphine and ziconotide as monotherapies for EIDD delivery for the treatment of chronic pain. Off-label pharmaceutical use and combination therapy for pain management are frequently documented (42).

Neuropathic, nociceptive, and mixed pain were each given their level of proof, according to the PACC 2017. In general, ziconotide, opioid plus local anesthetic, local anesthetic alone, clonidine plus opioid, and clonidine alone are effective treatments for neuropathic pain. Opioids, ziconotide, opioids plus local anesthetic, and local anesthetic alone are typically effective treatments for nociceptive pain. Cancer pain (localized and diffuse) is divided into two categories by PACC 2017: non-cancer pain (localized and diffuse) is also divided into two by PACC 2017. The PACC 2017 recommendations for cancer and non-cancer pain are shown in the following table

Table 1 Medication-selection recommendations and considerations for targeted implantable (intrathecal)drug delivery system (43)

Levels	Cancer or Other Terminal Condition-Related Pain with Localized Nociceptive or Neuropathic Pain.
Line 1A	Ziconotide and Morphine
Level 1B	Fentanyl Morphine or fentanyl + bupivacaine
Level 2	Hydromorphone, Hydromorphone + bupivacaine, Hydromorphone or fentanyl or morphine + clonidine Morphine or hydromorphone or fentanyl + ziconotide
Level 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine, Ziconotide + bupivacaine Ziconotide + clonidine Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide Sufentanil
Level 4	Sufentanil + ziconotide Sufentanil + bupivacaine Baclofen Sufentanil + clonidine Bupivacaine + clonidine + ziconotide Bupivacaine + clonidine
Level 5	Sufentanil + bupivacaine = clonidine
Level 6	Opioid* + bupivacaine + clonidine + adjuvants

	Cancer or Other Terminal Condition-Related Pain with Diffuse Nociceptive or Neuropathic Pain
Line 1A	Ziconotide, Morphine
Level 1B	Hydromorphone, Morphine or hydromorphone + bupivacaine
Level 2	Hydromorphone or morphine + clonidine, Morphine or hydromorphone + ziconotide
Level 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine Ziconotide + bupivacaine, Ziconotide + clonidine, Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide Sufentanil
Level 4	Sufentanil + ziconotide Baclofen, Sufentanil + bupivacaine, Sufentanil + clonidine Bupivacaine + clonidine + ziconotide Bupivacaine + clonidine
Level 5	Sufentanil + bupivacaine + clonidine, Sufentanil + bupivacaine + ziconotide, Sufentanil + clonidine + ziconotide
Level 6	Opioid* bupivacaine + clonidine + adjuvants
	Noncancer-related pain with Localized Nociceptive or Neuropathic Pain
Line 1A	Ziconotide, Morphine
Level 1B	Fentanyl, Fentanyl + bupivacaine
Level 2	Fentanyl + clonidine Hydromorphone or morphine + bupivacaine Fentanyl + bupivacaine + clonidine Bupivacaine
Level 3	Fentanyl + ziconotide + bupivacaine, Morphine or hydromorphone + clonidine, Ziconotide + clonidine or bupivacaine or both Bupivacaine + clonidine
Level 4	Sufentanil + bupivacaine or clonidine Baclofen, Bupivacaine + clonidine + ziconotide
Level 5	Sufentanil + bupivacaine + clonidine Sufentanil + ziconotide
	Noncancer-Related Pain with Diffuse Nociceptive or Neuropathic Pain
Line 1A	Morphine, Ziconotide*
Level 1B	Hydromorphone, Morphine or hydromorphone + bupivacaine
Level 2	Hydromorphone or morphine + clonidine Fentanyl + bupivacaine, Ziconotide + morphine or hydromorphone
Level 3	Hydromorphone or morphine + bupivacaine + clonidine, Fentanyl + ziconotide, Sufentanil + bupivacaine or clonidine, Ziconotide + clonidine or bupivacaine or both
Level 4	Fentanyl or sufentanil + bupivacaine + clonidine Sufentanil + ziconotide Baclofen
Level 5	Opioid* + ziconotide + bupivacaine or clonidine

- Ziconotide* should be the first choice in patients with >120 morphine equivalents or fast systemic dose escalation, in the absence of a history of psychosis,

- Opioid* (all known intrathecal opioids).

7. Cost-effectiveness of epidural and intrathecal delivery systems for chronic pain management

According to estimates, 43% of people have chronic pain, which places a big strain on their health and significantly lowers their quality of life when it comes to their health. As chronic pain is the second most frequent reason for requesting disability benefits, the financial burden is also considerable due to costs for medication, doctor visits, and other related expenses(44).

EIDDS are not only effective but also cost-effective, with Brogan et al. (45) demonstrating that the break-even point for IDDS for the management of refractory cancer pain occurs after six months of use due to lower drug expenditures and shorter hospital stays. Additionally, it was shown that IDDS therapy costs stabilized while those of traditional treatments continued to rise. Similar to this, Stearns et al. (30), using the Truven Health Market Scan Commercial Claims and Encounters Database, demonstrated that at 12 months, pharmacy costs were $9,264 higher for EIDDS while medical costs were $12,459 lower compared to conventional medical management (CMM), resulting in a total cost savings of $3,195 for EIDDS. The authors demonstrated more than $63,000 in cost savings after 12 months and more than $15,000 after two months of therapy with IDDS (rational) using the same database with more recent data (46), which covered the period from January 1, 2013, to September 30, 2019.

8. Complication

Although an implantable drug delivery system is a well-established method for treating chronic, severe pain, its dangers and side effects are just now starting to be more fully understood. The following are some of the complications of epidural and intrathecal drug delivery systems when we use them in the management of chronic pain (47-49):

Infection; The most severe complication, which may result in meningitis, an epidural abscess, or an infection of the spinal cord. Patients with a weakened immune system or those who have undergone prior spinal surgery are more likely to get an infection.

Bleeding; The use of anticoagulants, vascular lesions, inadequate hemostasis, and subsequent bleeding are all causes of bleeding. Swelling, pressure, and pain might result from bleeding with hematoma formation near the pump's insertion. Rapid action is necessary to address this issue.

Nerve damage; This could happen during the first surgery or afterward if the catheter kinks or is damaged. Pain, a lack of strength, numbness, or paralysis can result from nerve injury.

Overdose; This could happen if the patient unintentionally takes the pump's top off or if the pump has been improperly programmed. An overdose may result in coma, death, or respiratory depression.

Under dose; This could happen if the pump is improperly programmed or if the catheter is clogged. Pain, withdrawal symptoms, or other drug adverse effects may result from an under dose.

Device malfunctioning; If the pump or catheter isn't working properly, the drug may leak, cease working, or be administered in the incorrect amount. If a device problem is not identified and fixed, it could be fatal.

Additionally, allergic responses to the medication, headaches, nausea, and vomiting, dizziness, constipation, urinary retention, and skin irritation at the pump site are all potential side effects of epidural and intrathecal drug delivery systems. It is crucial to remember that these are just a few of the potential issues with intrathecal and epidural drug delivery systems.

Depending on the patient's unique characteristics and the exact conditions, the risk of each given problem will change(50).

9. Systems of epidural and intrathecal through an epidural or intrathecal delivery system

External system; This method consists of a tiny pump that is worn externally and a catheter that is inserted into the intrathecal or epidural area. When necessary, medication is replenished into the pump, and the rate of delivery can be changed. (50).

Implanted system; This device consists of a catheter that is inserted into the epidural or intrathecal space and a pump that is implanted under the skin. Through a port that is accessed through the skin, the pump is replenished with medication. A remote control can be used to change the delivery speed(51). The system used will rely on the specific requirements and preferences of the patient. External pump devices can be utilized for short-term treatment and are less intrusive. Fully implantable pump systems are more invasive, but they have the benefit of allowing the delivery rate to be changed without a trip to the doctor(52).

10. Implantation technique

The choice to place a pump is a complicated medical issue that needs thorough analysis, appropriate planning, and technical expertise. An implantation effectiveness test of the selected medication should be carried out before implanting an infusion pump (51). In the surgical room, the system must be implanted using strict aseptic procedures. Spinal anesthesia, regional anesthesia, or local anesthetic plus sedation are all options for doing the surgery. In some instances, general anesthesia will be used to carry out the procedure. Pulse oximetry, capnography, continuous ECG, and noninvasive blood pressure should all be used to monitor the patient as per normal practice. A prophylactic antibiotic should be given about 30 minutes before the procedure; our protocol calls for the intravenous administration of 2 g of cefazolin (50).

a) Intrathecal drug delivery system implantation method

Many people who experience chronic pain or suffer from cancer may find an intrathecal medication delivery device (pain pump) to be a wonderful, safe choice. There are far fewer side effects and reduced medication needs because the medicine is administered directly into the spinal fluid. A reservoir of medicine is implanted to supply at least one month's worth of treatment (40).

To place the catheter in the afflicted area of the spine, the providers make a small incision in the back. The real pump is then placed in the belly after an extension catheter is inserted under the skin from the spine around the torso. To ascertain whether the drug is efficient and whether a permanent pump is necessary, a trial intrathecal injection or temporary intrathecal pump is typically conducted. A catheter is used to administer the medication to the area surrounding the spinal cord, and the intrathecal pump itself is made of a metal pump that stores and delivers the medication. The drug can be delivered by the pump at various intervals during the day or with a slow release over some time (53).

b) Epidural drug delivery system implantation technique

Either the paramedian or midline approaches can be used to implant the epidural needle. In both situations, 1% lidocaine is injected into the region where the epidural needle is inserted. The needle is positioned in the midline between two spine processes when using the midline approach technique (54). The paramedian approach technique involves inserting the needle 1 cm laterally and 1 cm caudally from the lower border of the upper spinous process. Ligaments and soft tissue are penetrated with the epidural needle. The loss of resistance (LOR) syringe is used to locate the epidural space (55). By moving the needle attached to the syringe forward and pulling its plunger until the resistance is gone after the epidural space is reached, the syringe is filled with normal saline or air, and the resistance is measured. The LOR syringe is removed once the catheter is in the epidural space, and the epidural needle is then used to implant the catheter. Medication will be given by bolus or infusion using the catheter (56).

11. Patient satisfaction with EIDDS

The treatment of patients with persistent pain frequently involves targeted implantable drug delivery systems. The effectiveness of pain treatment, the decrease in opioid use, and the cost-efficiency of long-term pain management have all been demonstrated in previous studies. There aren't many studies looking at patient satisfaction with implanted pain pumps that are treated with specific intrathecal medicines (57).

One single-center survey study by Schultz, David M., et al. (58)shows that most patients reported improvements in their quality of life, physical function, and pain, as well as a decrease in their use of opioids after they started to use EIDDS. It was reported that 38.9% of patients had completely stopped taking oral opioids and continued taking only the EIDDS method. The position of the pump pocket was favorable to 91% of patients who were on the upper buttock pocket site overall. A viable option for long-term oral or skin patch opioid management, intrathecal TDD therapy can reduce pain and enhance the quality of life in patients with intractable pain. This research generally shows that patients with EIDD therapy express high levels of satisfaction. The clinical prognosis of individuals with complex chronic benign pain is still improved with intrathecal TDD treatment. Events involving mechanical failure, ineffectiveness, or the existence of comorbidities are factors that affect patient satisfaction. Quantifying the degree of improvements linked to the usage of TIDD therapy will require larger investigations in the future (59).

Another qualitative investigation on the effectiveness of implanted intrathecal pumps for chronic cancer-related pain was conducted by Hawley et al. (60). Six patients who also completed daily written questionnaires on pain and symptom management and perceived quality of life participated in a series of three semi-structured interviews. To determine the effect that caring for these patients had on the staff in a palliative care unit, interviews with nurses and doctors who were directly involved in the patients' care were also conducted. Even though their aspirations and expectations were not always fully realized, patients reported a significant decrease in their pain that had a profoundly good impact on their quality of life. Patients also indicated significant anxiety about relying on the gadget and a limited number of highly qualified people. The palliative care unit employees acknowledged that they had a big influence on the 'culture' of the facility. Both continual infusion management education and clear communication about the justification of the infusion were crucial. Following the intrathecal infusion, patients also needed continued palliative care to treat the mental, spiritual, emotional, and psychological components of their pain that were not controlled by it.

12. Challenges and Opportunities

a) Regulatory challenges for epidural and intrathecal delivery systems

The creation of novel EIDDSs that combine various technologies and medications has seen a fast surge in recent decades, with evident advantages. However, these goods pose an exceptional challenge for any health regulatory authority, including the US FDA, because of the novelty of these EIDDSs and the difficulty in determining the principal therapeutic benefit of such drugs(47).

The primary explanation is that health regulatory organizations categorize EIDDSs in various ways depending on the legal definition provided in the legislation they adhere to. Therefore, producers or sponsors cannot proactively foresee the regulatory classification of EIDDSs that combine multiple entities that are each designated as a medicine, biological product, or medical device. As a result, it might be difficult for manufacturers or sponsors to decide which regulatory channel they should use to distribute their EIDDS goods to clients (61). All regulatory processes are created to guarantee the effectiveness, safety, and caliber of products. Before granting the marketing approval, the developer should take these steps, such as determining the types of clinical and nonclinical trials necessary and the post-marketing quality standard requirements, such as Quality Systems for medical devices, current Good Manufacturing Practices for drugs, or both, such as the FDA's streamlined approaches for combination products.

Once more, the diversity of EIDDSs and the difficulty in determining the product's classification restrict the implementation of a single quality standard for all EIDDS products (62). Each EIDDS has unique requirements based on its purpose, intended application, and materials, pharmaceuticals, or biologics it contains; nonetheless, because all EIDDSs are administered parenterally, they must adhere to the quality control standards that apply to parenteral goods. The federal regulatory code has designated a few tools to assist developers in determining the quality testing necessary for their products. However, because the OCP has the final say in how combination products are categorized generally, a sponsor, manufacturer, or developer must have an early conversation with the OCP and the FDA's centers to get support and feedback for the creation of any EIDDS. Any sponsor or producer must be aware of the applicable regulatory framework for such products as well as any potential measures that may be done to enhance the effectiveness and efficiency of the regulatory process for a particular product (63). Early communication with the FDA and its centers is essential to efficiently plan and advance along the regulatory pathway, even though future opportunities to support and clarify this regulatory process must be encouraged (61).

b) Ethical Challenges for Targeted Implantable Delivery Systems

There are several implantable medical devices available today. It has been thought that the type of implants that connect with body tissues has particularly serious ethical consequences (64). Some of these ethical concerns are being addressed by the "EPIONE" project, which is financed by the EU. The initiative is attempting to enhance the safety and efficiency of these devices while also providing recommendations for the moral use of implantable medication delivery systems. This review discussed some of them (64, 65);

Privacy: The information gathered by implantable medication delivery systems may be used to track patients without their permission or to exclude them from insurance coverage or the workforce. For instance, an insurance provider or an employer may utilize information from a patient's implantable drug delivery system to refuse them coverage or a job.

Informed consent: Patients who receive implantable medication delivery systems might not be completely aware of the dangers and negative effects of the medical technology. They might not be aware that they can be removed, turned off, or eventually need to be replaced. Patients may choose treatments that are not in their best interests as a result of this lack of informed consent.

Cost: Patients may not be able to purchase implantable drug delivery systems because of their high cost. Patients may be required to pay for these gadgets out of pocket if insurance companies do not cover their costs. The high price of implantable drug delivery devices may make it impossible for some patients to receive the necessary care.

Safety: Because implantable medication delivery systems are still being developed, there is a chance that they could break down or become infected. Patients have occasionally lost their lives as a result of complications with these devices. Implantable drug delivery devices' potential for damage may deter patients from receiving the necessary care.

c) Future opportunities for epidural and intrathecal delivery systems

Compared to conventional methods of administration, medication implant technology can deliver drugs more precisely, locally, and for longer periods, with fewer adverse effects (66). For more than 30 years, epidural and intrathecal drug delivery devices (EIDDS) have been utilized to treat chronic pain. Compared to conventional pain relief techniques like oral pills and injections, these systems have several benefits, including improved accuracy and efficiency of medication delivery, less chance of adverse effects, and improved patient compliance (12). Future applications for EIDDS technology in chronic pain management are numerous as the technology develops. These consist of (13, 67-69):

Use of new drugs and drug combinations; Numerous medications, such as opioids, local anesthetics, and anticonvulsants, can be administered with EIDDS. when new drugs are developed for chronic pain, EIDDS can be the best way to deliver these drugs in a more effective and targeted way.

The use of personalized medicine; According to the requirements of each patient, EIDDS can be utilized to provide medications in a tailored manner. This can entail using genetic testing to pinpoint individuals who are more likely to respond to particular medications or using real-time monitoring to modify drug administration based on the patient's level of discomfort.

The development of wireless EIDDS; Current EIDDS systems demand that patients refill their drug reservoirs at a doctor's office. Wireless EIDDS would enable patients to top out their reservoirs at home, increasing convenience and lowering treatment costs.

A bright future is provided by EIDDS for the treatment of chronic pain. EIDDS are probably going to get cheaper, more practical, and more efficient as technology develops (13).

The potential for developing targeted implantable medication delivery systems to treat chronic pain is enormous. These systems are designed to deliver drugs in a sustained and controlled manner, avoiding systemic administration and minimizing any potential negative effects. Nanotechnology and materials science developments have made it possible to create implanted devices with precise and regulated medication delivery capabilities. For the best pain treatment for specific individuals, these devices can be configured to deliver medication at specified times and in specific amounts (70, 71).

The creation and broad application of targeted implantable medication delivery devices for chronic pain, however, face several obstacles. These comprise assuring the implant's long-term stability and biocompatibility, creating trustworthy techniques for observing and modifying medication release, and resolving potential problems such as device migration or infection. Despite these difficulties, efforts are being made to advance the field of tailored implanted medication delivery devices for chronic pain through ongoing research and development. These technologies have the potential to transform pain management and improve the quality of life for those with chronic pain with additional invention and improvement (72).

Conclusion

Using epidural and intrathecal drug delivery devices (EIDDS) to alleviate chronic pain is a promising strategy. These systems make it possible to deliver medication right to the location of the pain, which might assist in lowering the dosage needed and lessen adverse effects. Additionally, EIDDS can be set up to dispense medication according to a specified schedule, helping to guarantee that patients get the proper medication at the right time. Numerous high-quality randomized controlled trials and economic analyses have been used to assess its efficacy, safety, and cost-effectiveness. All forms of pain, including those that are still challenging to treat with traditional methods, can now be targeted with devices and treatments. EIDDS significantly lowers the hazards related to systemic therapies, such as opioids, for refractory cancer pain. With implantations performed by specialized facilities, refills administered by compounding pharmacies, and follow-ups handled by advanced nurse practitioners closer to patients' homes, the limited access to EIDDS therapy may be improved. Research activities and novel techniques are currently being conducted in the field of implantable drug delivery systems. Researchers are still optimistic that many of these systems will eventually be created with optimal zero-order release kinetics profiles that would work well in vivo for lengthy periods and allow for prolonged use in a patient with chronic pain. EIDDS is a promising new treatment option for chronic pain treatment.

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Research Article

Evaluating the Nephroprotective and Hepato-protective Effects of Hypoestes rosea in Acetaminophen-Induced Toxicity in Albino Rats

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Abstract:

The leaves of Hypoestes rosea are in use as traditional medicine in the Niger Delta areas in Nigeria and the Western part of Cameroun for the management of different ailments in children, such as anaemia, malaria, fever and other ailments. Regardless of its uses, scanty studies evaluating its organ protective effects exist. Therefore, this research study evaluates the nephroprotective and hepato-protective effects of Hypoestes rosea in acetaminophen-induced toxicity in Albino rats. The objectives of this research study are to evaluate the protective effect of Hypoestes rosea on the kidney and the liver of albino rats. Acetaminophen, which is frequently used as an analgesic and antipyretic drug at high doses, can be harmful to vital organs of the body, affecting the liver and kidneys. In this study, effects of an aqueous extract of Hypoestes rosea (AEHr) on liver function parameters and kidney function parameters of acetaminophen induced-toxicity in albino rats were evaluated using acute (15 days) and sub-chronic (30 days) duration of study and study group comprising of prophylactic (pre-treatment) and therapeutic (post-treatment) phases with six experimental groups in each phase. A total of 112 adult apparently healthy Albino rats weighing (180-220g) were used for this study, divided into six experimental groups of extract control (EC), negative control (NC), positive control (PC), AEHr100mg/kg b w., AEHr 200mg/kg b w., and AEHr 300mg/kg b w. groups each of six rats. At the end of the research study period, blood samples were collected through jugular puncture for liver and kidney function parameters. Results showed that acetaminophen-induced toxicity in albino rats caused toxicity to the kidney and toxicity to the liver, as evidenced by the raised levels of potassium, urea, creatinine and low bicarbonate from the renal function parameters and also as evidenced by significant elevation of bilirubin and liver enzymes with a significantly low total protein and albumin levels from the liver function parameters when compared with other experimental groups. Conversely, AEHr at different concentrations in a dose-dependent pattern at the different treatment phases and different duration periods were able to repair the injury to the kidney and liver caused by acetaminophen induction to normal. Consequently, the findings of this research propose that Hypoestes rosea contains active ingredients accountable for the nephroprotective and hepato-protective abilities in rats and can be recommended for more studies using higher mammals.

Keywords: Hypoestes rosea, acetaminophen, nephroprotective, aqueous extract of Hypoestes rosea (AEHr), hepato-protective, liver function parameters, kidney function parameters

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1. Introduction

The kidneys are vital organs that function in maintaining homeostasis, which is made possible with the management of fluid levels, electrolyte balance, waste excretion,

reabsorption of nutrients, maintaining pH, osmolality, regulation of blood pressure and secretion of active compounds. It is prone to stimuli or drugs causing nephrotoxicity (1).

The liver is also a vital organ essential for maintaining homeostasis and metabolic integrity in the body, harbouring important functions associated with the regulation of carbohydrate, lipid, amino acid, and hormone metabolism, synthesis and degradation of plasma proteins, glycogen synthesis, storage of vitamins and metals, secretion of bile, xenobiotic metabolism and playing a major role in the metabolism and removal of drugs among others. (2).

Several studies have demonstrated the induction of hepatocellular and or renal damage by acetaminophen overdose in experimental animals and humans. (3). Drug-induced nephrotoxicity is increasingly recognized as a significant contributor to kidney disease, including acute kidney injury (AKI) and chronic kidney disease (CKD). Nephrotoxicity has a wide spectrum, reflecting damage to different nephron segments based on individual drug mechanisms. (4). Both glomerular and tubular injuries are known targets for drug toxicity and may result in acute or chronic functional changes (5). Acetaminophen is generally safe at recommended doses, but because the drug is available without prescription, it is potentially more dangerous than other similar drugs when used in excess or overdose (6). Metabolically, acetaminophen is detoxified in the liver by oxidation through a minor cytochrome p450 mediated pathway to produce a highly reactive cytotoxic metabolite, N-acetyl benzoquinone mine (NAPQI), which liver-reduced glutathione (GSH) converts to a water-soluble, harmless product, mercapturic acid, (7). The liver defence system succumbs to acetaminophen drug burden following the depletion of glutathione to pave the way for NAPQI accumulation, and oxidative stress ensues (8)

Natural plant products and their derivatives or herbal drugs have gained importance and popularity in recent years because they are considered safe, efficacious, and cheap (9). Therefore, interest in the utilization of alternative medicines for the treatment of renal and hepatic diseases has increased (10) since renal and liver diseases are important problems all over the world, and they are increasing day after day. Plants have been used as a folkloric source of medicinal agents since the beginning of mankind. *Hypoestes rosea* is one such plant with acclaimed folk medicinal usage and is reported to possess anti-inflammatory, anticancer, antimalarial, and antioxidant properties (6,9,11,12,13). The leaves are, therefore, medicinal plant products since they contain active organic ingredients that are employed in the treatment of diseases.

Hypoestes rosea, commonly called 'polka dot plant', 'freckle face' and 'morning glory lobelia' is a broad-leafed flowering evergreen plant that belongs to the kingdom; Plantae, Phylum; Tracheophyta, class; Magnoliopsida, order; Lamiales, family; Acanthaceaa, subfamily; Acanthoideae, Tribe; Ruellieae, sub-tribe; Justiciinae and genus *Hypoestes*. *Hypoestes phyllostachya 'rosea'* is a tropical sub-shrub native to Madagascar but found in most parts of the world, especially West Africa. It has scientifically been proven to contain phytochemicals such as flavonoids, diterpenes and sterols, balsam, carbohydrates, monosaccharides reducing sugars, tannins and saponins (14).

However, there has not been adequate scientific data to support the nephroprotective and hepato-protective potentials of *Hypoestes rosea* and provide information on its mechanism of action. This study, therefore, provides information on the ability of aqueous extract of *Hypoestes rosea* leaves to protect the kidney and the liver against acetaminophen-induced hepatocellular damage in albino rats.

2. Materials and Methods

2.1 Plant Collection, Identification and Authentication

Fresh *Hypoestes rosea* leaves were collected from Ulakwo -1 in Etche LGA (4°59' 27.00" N, 7°03 16 00"E) Rivers state in Nigeria. It was identified by Dr. Osiyemi Seun on 22/04/2019 with FHI no. 112295 at the Taxonomy section of the Forest herbarium unit in the Forestry Research Institute of Nigeria, Ibadan.

2.2 Method of Extraction and Preparation of AEHr

The leaves of *Hypoestes rosea* were removed from the stem, washed and air dried under shade at room temperature for fourteen days (2 weeks) and then milled into powder. 450g of Hypoestes rosea powder was macerated in 1000 ml of water to dissolve for 48 hours in a flask; the extract was decanted and then filtered through Whatman No. 1 filter paper to obtain a clear extract. The aqueous extract was further concentrated at 60°C using a rotary evaporator and dried using a freezer drier. The resulting crude extract, which weighed 214 g, was stored in a refrigerator maintained at 4-18°C until the analysis was over. The extracts were later weighed and reconstituted in distilled water to give the required doses of 100, 200 and 300 mg/kg body weight that were used in the study.

2.3 Collection of Experimental Animals and Acclimatization

Albino rats were considered the animals of choice for this study because of their availability, cost, genetic makeup, handling technique and the nature of the study. Adult, apparently healthy albino rats weighing (180 – 220 grams) were used. The rats were purchased from the Experimental Animal Unit of the Department of Human Physiology, University of Port-Harcourt. The rats were contained in conservative wire mesh cages under standard laboratory conditions. After the collection of the animals, they were weighed, identified and kept in wire gauge cages under favourable conditions for two weeks. The animals were receiving food and water libitum and handled regularly so as to acclimatize with the environment. One hundred and fifty-six (112) albino rats 12 weeks old rats were used in this study. All animal handling protocols were in accordance with institutional guidelines for laboratory animals. (Ethic Reference Number PM/27/08/2011/MAA (R) and OECD guidelines.

2.4 Reagent's Requisition and Preparation

Acetaminophen was purchased from Sigma Aldrich. They were prepared following standard procedures.

2.5 Experimental Design

2.5.1 Animal grouping

A total of one hundred and twelve (112) adult albino rats were assigned by weight into eighteen (18) groups and allowed to acclimatize for (fourteen) 14 days (2 weeks). The duration of the study was fifteen (15) days acute and thirty (30) days sub-chronic study. Eight (8) albino rats each were assigned to the two (2) positive control groups, and six (6) albino rats each were assigned to the other groups.

2.5.2 Experimental Grouping and Treatment Regimen

The study groups comprised two treatment phases, prophylactic (Pre-treatment) and therapeutic (Post-treatment) phases, and duration of treatment (Acute and sub-chronic), with six experimental groups in each of the phases. In the prophylactic (pre-treatment) phases, the Albino rats were administered with AEHr before acetaminophen induction, while in the therapeutic (post-treatment) phases, the Albino rats were treated with AEHr after acetaminophen induction. The groups are as follows:

Group 1. Negative control (NC): Apparently, healthy rats received de-ionized water and normal feed only.

Group 2. Positive control (PC): 500mg/kg b w. acetaminophen-induced rats on the 14th day in acute and the 29th day in the Sub-chronic study.

Group 3. Extract Control (EC): Apparently, healthy rats that received AHEr 100mg/kg b w. orally daily for fifteen (15) days and thirty (30) days.

Group 4. Acetaminophen-induced treatment group aqueous extract of Hypoestes rosea of 100 mg/kg b w.

Group 5. Acetaminophen-induced treatment group aqueous extract of Hypoestes rosea of 200 mg/kg b w.

Group 6. Acetaminophen-induced treatment group aqueous extract of Hypoestes rosea of 300 mg/kg b w.

2.6 Sample collection

Rats were anaesthetized using chloroform and were sacrificed on the 15th and the 30th days after an overnight fast. Blood samples were collected by puncture of the jugular vein and put into lithium heparin bottles for analyses of liver and renal function parameters.

2.7 Laboratory analysis

The laboratory analysis was done using a Mindray Biochemical analyzer (Model BS 120) using a timed endpoint at the Research Laboratory of the Departments of Biochemistry and Physiology, University of Port-Harcourt, Port-Harcourt.

2.8. Quality Control

Quality was adhered to following standard operating procedures and good laboratory and best practices.

2.9 Ethical consideration

This study was carried out in accordance with the Guidelines of the Organization for Economic Cooperation and Development (OECD) 2001, and ethical approval was obtained from the University and Departmental Committee for Research and Ethics, University of Port Harcourt.

2.10 Data Analysis

Data were analyzed using SPSS version 23, and they were presented as Mean ±SEM. Variations between them were determined using analysis of variance (ANOVA) and Tukey Test of Multiple Comparison, which were used to differentiate variations in means between groups. P-values less than 0.05 ($P<0.05$) were considered statistically significant.

3. Results and Discussion

The results of acute and sub-chronic effects of various concentrations of aqueous extract of Hypoestes rosea (AEHr) on liver function parameters in acetaminophen-induced albino rats by treatment phase and experimental groups are shown in Tables 1-2

The medicinal effects of Hypoestes rosea, like other plants, may be attributed to the presence of active bio-ingredients or phytochemicals in them, which are generally responsible for preventing disease and promoting health. (15). Hypoestes rosea leaves are, therefore, medicinal plant products since they contain active organic ingredients that are employed in the treatment of diseases. It possesses anti-inflammatory, anticancer, anti-malarial and antioxidant effects. (7-9 &12-13). Acetaminophen is generally safe at recommended doses, but because the drug is available without prescription, it is potentially more dangerous than other similar drugs when used in excess or overdose (6). Acetaminophen-induced hematotoxicity and nephrotoxicity in experimental animals was well recognized and reported (16). The liver is a known organ where activation and detoxification of acetaminophen takes place; therefore, it is very susceptible to being damaged by acetaminophen toxicity (17 -18). In this respect, hepatoprotective effects were evaluated using hepatic function parameters of total bilirubin, conjugated bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH), 5' nucleotidase (5'NT), total protein and albumin. Findings show that the liver was disrupted in positive control group rats given acetaminophen than in negative control and extract control group rats, indicating hepatotoxic effects of acetaminophen. This also agrees with (18) and (19) studies on the protective effect of some Egyptian medicinal plants against oxidative Stress in Rats. The significant increase in total bilirubin, conjugated bilirubin, and serum liver enzymes ALT, AST, ALP, GGT, 5'NT, and LDH activities, which were reported in the acetaminophen treated group (Positive control group) reflects hepatocellular injury and the leakage of enzymes from cytoplasm into blood indicating cell necrosis and inflammatory reactions (20-21). The more specific cytosolic AST, found in high concentration in the liver, and ALT,

which is localized in the cytosol and mitochondria, are released into the circulation in the early phase of liver injury (22). Prolonged destruction of the hepatic cells results in more hepatic releases to exacerbate hepatic dysfunction and causes an elevation in the serum levels of ALP, GGT, 5'NT and LDH.

However, the reduction of serum proteins and albumin evidenced in the study in the positive control group may be due to a decreased number of functional hepatocytes or due to possible nephrotoxicity, which leads to leakage of albumin in urine with decreasing serum albumin and total protein concentration (6). The observed elevation of TB. CB, ALT, AST, ALP, GGT, 5'NT and LDH due to acetaminophen toxicity and challenge agree with the findings of (23-24) in which, respectively, hepatoprotective effects of ajoene from garlic, leaf extract of Wedelia calendulacea and Garcinia kola seed with Vitamin E. against acetaminophen-induced hepatic damage were found. The observed dose-dependent reversal of acetaminophen-induced alterations in the liver enzymes and bilirubin levels by pre-administration and post-administration of aqueous extract of Hypoestes rosea suggests that this plant is hepatoprotective.

Similarly, the results of acute and sub-chronic effects of various concentrations of AEHr on renal function parameters in acetaminophen induced albino rats by treatment phases and experimental groups are presented in Tables 3- 4.

Also, considering the administration of albino rats with acetaminophen at a dose of 500 mg/kg.b wt. in the acute and sub-chronic study, results showed significant alterations in kidney function, which was evaluated in this study by assessing serum levels of potassium, sodium, bicarbonate, chloride, urea and creatinine in the control and experimental groups. In the positive control group, a significant decrease in serum values of bicarbonate was observed, along with a significant increase in potassium, urea, and creatinine, when compared to the negative and extract control groups. This could be explained by renal dysfunction in the positive control group rats (25). This implies that acetaminophen has a nephrotoxic effect due to its oxidative stress effect on renal tissue, as confirmed by (26). However, treatment with various concentrations of aqueous extract of Hypoestes rosea to acetaminophen-induced groups significantly increased levels of bicarbonate and decreased the levels of potassium, urea and creatinine to normal control values. As also reported by (27) on medicinal plants. It is, therefore, also established that Hypoestes rosea possesses a nephroprotective effect through its potent antioxidant potential and effect protecting the kidney against damage caused by various nephrotoxic agents such as acetaminophen.

Table 1 (a): Acute Effects of Various Concentrations of Aqueous Extract of *Hypoestes rosea* (AEHr) on Liver Function Parameters of Acetaminophen-Induced Albino Rats by Treatment Phase and Experimental Group.

Experimental groups	TB (µmol/L) Mean ± SEM	CB (µmol/L) Mean ± SEM	ALT (IU/L) Mean ± SEM	AST (IU/L) Mean ± SEM	GGT (IU/L) Mean ± SEM	ALP (IU/L) Mean ± SEM
Prophylactic (Pre-Treatment)						
EC	5.97±0.17^{a}	4.47±0.56^{a}	13.45±0.69^{a}	31.17±2.89^{a}	20.33±0.80^{a}	67.50±7.34^{a}
NC	6.37±0.46^{a}	3.77±0.31^{a}	8.75±0.36^{b}	24.17±3.21^{b}	22.67±1.84^{a}	45.00±1.92^{b}
PC	25.50±3.18^{b}	6.05±0.67^{b}	23.83±3.85^{c}	64.83±7.78^{c}	51.33±2.72^{b}	76.50±10.26^{c}
AEHr (100mg/kg)	7.90±0.83^{a}	5.27±0.33^{b}	9.60±0.47^{b}	44.83±5.96^{d}	30.67±1.99^{c}	30.33±1.86^{d}
AEHr (200mg/kg)	6.08±0.34^{a}	3.18±0.19^{ac}	16.07±1.11^{d}	33.67±2.06^{a}	21.67±1.48^{a}	36.17±1.60^{d}
AEHr (300mg/kg)	5.50±0.33^{a}	2.78±0.19^{ac}	14.62±1.08^{d}	21.67±2.36^{e}	18.00±1.36^{a}	32.67±2.84^{d}

F-ratio	33.00	9.08	11.73	42.97	50.25	50.29
P-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001****
Therapeutic (Post Treatment)						
EC	5.97±0.17^{a}	4.47±0.56^{ab}	13.45±0.69^{a}	31.17±2.89^{a}	20.33±0.88^{a}	67.50±7.34^{a}
NC	6.37±0.46^{a}	3.77±0.31^{a}	8.75±0.36^{b}	24.17±3.21^{b}	22.50±1.80^{a}	45.00±1.92^{b}
PC	25.50±3.18^{b}	6.05±0.67^{b}	23.83±3.85^{c}	64.83±7.78^{c}	51.33±2.72^{b}	76.50±10.26^{c}
AEHr (100mg/kg)	7.07±0.71^{a}	5.85±0.50^{ab}	9.73±0.43^{b}	49.83±3.96^{d}	27.33±2.42^{c}	30.67±1.84^{d}
AEHr (200mg/kg)	7.30±0.52a	4.30±0.22a	17.10±1.42^{d}	38.50±1.38^{e}	19.50±0.99^{ac}	34.33±1.76^{d}
AEHr (300mg/kg)	6.88±0.45^{a}	3.10±0.14^{ac}	14.33±0.86^{e}	27.00±3.62^{f}	15.33±1.12^{a}	35.00±2.70^{d}
F-Ratio	34.67	9.246	13.23	46.5	52.35	57.24
P-value	<0.0001****	<0.0001****	<0.0001****	<0.0001****	<0.0001****	<0.0001****

Abbreviations: SEM: Standard Error of Mean; TB:Total Bilirubin, CB:Conjugated Bilirubin, ALT: Alaninine Amino Transaminase, AST: Aspartate Transaminase, GGT: Gamma Glutamyl Transaminase, ALP: Alkaline Phosphatase,.Experimental Groups: Extract Control (EC), Negative Control (NC), Positive Control (PC), Aqueous Extract of *Hypoestes rosea* at 100 mg/kg (AEHR (100 mg/kg)), AEHR (200 mg/kg), AEHR (300 mg/kg). Treatment Phases: Prophylactic (Pre-Treatment), Therapeutic(Post-Treatment). N for each level mean=12.Within treatmentphases by experimental groups, each parameter means ± SEM with different superscripts are significantly different at p<0.05. Significance Level: ****=p<0.0001.

Table 1 (b): Acute Effects of Various Concentrations of Aqueous Extract of *Hypoestes rosea* (AEHr) on Liver Function of Acetaminophen-Induced Albino Rats by Treatment Phase and Experimental Group

Treatment Phases	**Experimental Group**	**5'NT (IU/L) Mean ± SEM**	**LDH (IU/L) Mean ± SEM**	**TP (g/dL) Mean ± SEM**	**ALB (g/dL) Mean ± SEM**	**AST/ALT Ratio Mean ± SEM**
Prophylactic (Pre-Treatment)	EC	0.82±0.12^{a}	115.00±4.03^{a}	65.33±1.45^{a}	40.17±1.17^{a}	1.54±0.19
	NC	0.68±0.18^{a}	127.50±2.74^{a}	64.83±1.74^{a}	38.33±0.99^{ab}	2.06±0.39
	PC	2.08±0.34^{b}	207.5±3.40^{b}	53.50±1.45^{b}	37.50±1.43^{ab}	1.43±0.11
	AEHr (100mg/kg)	1.00±0.10^{a}	114.20±4.72^{a}	65.67±1.54^{a}	42.17±1.70^{a}	1.16±0.11
	AEHr (200mg/kg)	0.96±0.10^{a}	112.30±5.82^{a}	67.50±0.89^{ac}	38.83±1.33^{a}	1.14±0.14
	AEHr (300mg/kg)	0.98±1.15^{a}	112.30±4.75^{a}	71.33±1.63^{c}	41.33±1.54^{a}	0.95±0.04
Test Statistics	F- Ratio	8.67	74.72	21.18	24.09	4.104
	P- value	<0.0001****	<0.0001****	<0.0001****	<0.0001****	0.0059**
Therapeutic (Post Treatment)	EC	0.82±0.12^{a}	115.00±4.03^{a}	65.33±1.45	40.17±1.17^{a}	1.54±0.19
	NC	0.68±0.18^{a}	127.50±2.74^{a}	64.83±1.74	38.33±0.99^{a}	2.06±0.39
	PC	1.88±0.36^{b}	207.50±3.40^{b}	53.50±1.38	32.50±1.34^{ab}	1.43±0.11
	AEHr (100mg/kg)	0.96±0.11^{a}	126.00±6.23^{a}	67.33±1.36	40.33±1.12^{a}	1.21±0.10
	AEHr (200mg/kg)	0.98±0.10^{a}	127.50±9.00^{a}	73.67±0.67	44.33±1.12^{c}	1.10±0.11

	AEHr (300mg/kg)	0.97±0.19[a]	120.50±6.49[a]	74.67±0.84	45.83±1.08[c]	0.91±0.04
Test Statistics	F-Ratio	11.67	36.69	42.81	17.23	4.454
	p-value	<0.0001****	<0.0001****	<0.0001****	<0.0004****	0.0037**

Abbreviations: SEM: Standard Error of Mean; 5'NT: 5' Nucleotidase; LDH: Lactate Dehydrogenase; TP: Total Protein, ALB: Albumin; AST/ALT ratio. Experimental Groups: Extract Control (EC), Negative Control (NC), Positive Control (PC), Aqueous Extract of Hypoestes rosea at 100 mg/kg (AEHR (100 mg/kg)), AEHR (200 mg/kg), AEHR (300 mg/kg). Treatment Phases**:** Pre-Treatment, Post-Treatment. N for each level mean=12.Within and across treatment phases by experimental groups, each parameter means ± SEM with different superscripts are significantly different at p<0.05. Significance Level: ****=p<0.0001; ns=Not Significant (p>0.05)

Table 2 (a): Sub-Chronic Effects of Various Concentrations of Aqueous Extract of *Hypoestes rosea* (AEHr) on Liver Function Parameters of Acetaminophen-Induced Albino Rats by Treatment Phase and Experimental Group.

Treatment Phases	**Experimental Group**	**TB (µmol/L) Mean±SEM**	**CB (µmol/L) Mean±SEM**	**ALT (IU/L) Mean±SEM**	**AST (IU/L) Mean±SEM**	**GGT (IU/L) Mean±SEM**	**ALP (IU/L) Mean±SEM**
Prophylactic (Pre-Treatment)	EC	5.90±0.24[a]	4.65±0.57[b]	12.67±0.67[a]	19.00±3.03[a]	18.17±0.98[a]	45.33±3.29a
	NC	6.10±0.69[a]	2.93±0.37[a]	9.00±0.52[a]	21.67±0.92[a]	19.83±1.85[a]	51.33±3.25b
	PC	12.83±1.42[b]	5.22±0.41[b]	35.83±2.34[b]	44.83±4.03[b]	47.67±3.16[b]	58.33±8.83c
	AEHr(100mg/kg)	7.35±1.65[c]	5.50±0.38[b]	19.50±0.89[c]	19.67±2.06[a]	24.33±2.32[c]	47.00±4.16a
	AEHr(200mg/kg)	6.52±0.35[a]	5.82±0.32[b]	14.33±0.85[ac]	21.33±2.11[a]	17.00±0.97[a]	40.50±3.10d
	AEHr(300mg/kg)	7.10±0.55[ac]	5.20±0.17[b]	14.17±1.17[c]	17.67±2.57[c]	12.83±0.98[d]	39.00±2.56d
Test Statistics	F- ratio	32.24	12.15	60.60	45.8	43.39	57.05
	P – value	<0.0001****	0.004***	<0.0001****	<0.0001****	<0.0001****	<0.0001****
Therapeutic (Post-Treatment)	EC	5.90±0.24[a]	4.65±0.57[b]	12.67±0.67[a]	19.00±3.03[a]	18.17±0.98[a]	45.33±3.29[a]
	NC	6.10±0.69[a]	2.93±0.37[a]	9.00±0.52[a]	21.67±0.92[a]	19.83±1.85[a]	51.33±3.25[b]
	PC	12.83±1.42[b]	5.22±0.41[b]	35.83±2.34[b]	44.83±4.03[b]	47.67±3.16[b]	58.33±8.83[c]
	AEHr(100mg/kg)	7.10±1.12[c]	5.23±0.21[b]	16.67±1.52[c]	20.50±2.28[a]	21.83±2.34a	26.67±4.46[d]
	AEHr(200mg/kg)	7.03±0.67[c]	4.75±0.18[b]	10.67±0.68[a]	22.00±2.38[a]	13.50±0.81[c]	27.67±2.49[d]
	AEHr(300mg/kg)	5.90±0.24[a]	5.22±0.26[b]	11.73±1.22[a]	18.00±1.57[a]	11.00±1.03[c]	21.83±2.1[e]
Test Statistics	F-Ratio	2.79	14.24	60.98	55.12	48.46	62.38
	P-value	0.0349**	<0.0049***	<0.0001****	<0.0001****	<0.0001****	<0.0001****

Table 2 (b): Sub-Chronic Effects of Various Concentrations of Aqueous Extract of *Hypoestes rosea* (AEHr) on Liver Function Parameters of Acetaminophen-Induced Albino Rats by Treatment Phase and Experimental Group.

Treatment Phases	Experimental Group	5'NT (IU/L) Mean ± SEM	LDH (IU/L) Mean ± SEM	TP (g/dL) Mean ± SEM	ALB (g/dL) Mean ± SEM	AST/ALT RATIO Mean ± SEM
Prophylactic (Pre-Treatment)	EC	0.71±0.08^{a}	111.30±4.12^{a}	61.50±1.73^{a}	40.17±2.10^{a}	1.53±0.24^{a}
	NC	0.68±0.13^{a}	123.70±2.09^{a}	62.00±1.55^{a}	39.33±2.50^{a}	2.04±0.37^{a}
	PC	1.33±0.14^{b}	207.30±4.22^{b}	46.83±2.09^{b}	31.83±3.15^{b}	1.43±0.11^{a}
	AEHr (100mg/kg)	0.82±0.15^{a}	121.30±6.47^{d}	72.67±0.95^{c}	31.67±1.09^{b}	1.12±0.12^{b}
	AEHr (200mg/kg)	0.96±0.14^{a}	122.50±9.11^{d}	69.67±1.23^{c}	29.00±3.07^{b}	1.14±0.13^{b}
Pre-Treatment	AEHr (300mg/kg)	1.01±0.14^{a}	114.80±5.52^{d}	62.17±0.70^{a}	33.00±1.44^{b}	0.96±0.05^{b}
Test Statistics	F-Ratio	4.159	41.11	38.06	8.321	3.792
	p-value	0.0055**	<0.0001****	<0.0001****	<0.001***	0.0088**
Therapeutic (Post-Treatment)	EC	0.71±0.08^{a}	111.30±4.12^{a}	61.50±1.73^{a}	40.17±2.10^{a}	1.53±0.24^{a}
	NC	0.68±0.13^{a}	123.70±2.09^{a}	62.00±1.55^{a}	39.33±2.50^{a}	2.04±0.37^{a}
	PC	1.33±0.14^{b}	207.30±4.22^{b}	46.83±2.09^{b}	31.83±3.15^{b}	1.43±0.11^{a}
	AEHr (100mg/kg)	1.16±0.16^{a}	100.30±2.89^{a}	70.17±1.05^{c}	36.67±1.31^{a}	1.26±0.13^{a}
	AEHr (200mg/kg)	1.28±0.21^{b}	103.00±3.30^{a}	66.00±1.51^{c}	37.33±1.50^{a}	1.27±0.11^{a}
	AEHr (300mg/kg)	1.04±0.17^{a}	97.33±7.28^{a}	60.17±0.54^{ad}	41.17±2.18^{a}	1.09±0.10^{b}
Test Statistics	F-Ratio	4.646	94.96	44.59	31.42	2.655
	p-value	0.0029**	<0.0001****	<0.0001****	<0.0045***	0.0421

Table 3: Acute Effects of Various Concentrations of Aqueous Extract of *Hypoestes rosea* (AEHr) on Renal Function Parameters of Acetaminophen-Induced Albino Rats by Treatment Phase and Experimental Groups

Treatment Phase	Experimental Group	K+ (mmol/L)	Na+ (mmo/L)	Cl - (mmol/L)	HCO3- (mmol/L)	Urea (mmol/L)	Creatinine (mmol/L)
		Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	Mean ± SEM
Prophylatic (Pre-Treatment)	EC	4.63±0.10^{a}	147.33±5.25	104.00±2.38	26.17±0.70^{a}	3.23±0.16^{a}	68.17±1.47^{ad}
	NC	4.47±0.30^{a}	140.50±3.79	97.00±4.08	23.50±0.62^{a}	4.27±0.17^{a}	74.67±1.67^{a}
	PC	6.57±0.17^{b}	137.50±1.41	104.17±1.64	20.17±1.35^{b}	10.77±0.51^{b}	210.80±10.83^{b}
	AEHr (100mg/kg)	4.77±0.88^{a}	139.50±1.09	104.00±2.07	26.67±0.84^{a}	5.07±0.22^{a}	98.33±3.19^{cd}
	AEHr (200mg/kg)	4.23±0.13^{a}	140.83±1.96	102.83±2.15	26.00±1.13^{a}	4.62±0.17^{a}	88.50±2.57^{d}
	AEHr (300mg/kg)	4.02±0.07^{a}	140.00±2.07	103.33±1.20	26.17±1.05^{a}	3.65±0.21^{a}	83.33±1.26^{d}
Test Statistics	F-Ratio	31.66	0.5956	1.30	6.608	106.9	121.8
	P-value	<0.0001****	0.7035^{ns}	0.2903	0.0003***	<0.0001****	<0.0001****
Therapeutic(Post-Treatment)	EC	4.63±0.10^{a}	147.33±5.25	104.00±2.38	26.17±0.70^{a}	3.23±0.16^{a}	68.17±1.47^{ad}
	NC	4.47±0.30^{a}	140.50±3.79	97.00±4.08	23.50±0.62^{a}	4.27±0.17^{a}	74.67±1.67^{a}
	PC	6.57±0.17^{b}	137.50±1.41	104.17±1.64	20.17±1.35^{b}	10.77±0.51^{b}	210.80±10.83^{b}
	AEHr (100mg/kg)	4.32±0.12^{ad}	137.17±2.93	97.002±4.08	24.33±0.67^{a}	4.77±0.20^{a}	89.83±3.06^{cd}
	AEHr (200mg/kg)	3.18±0.13^{ad}	140.67±2.91	104.00±2.38	22.33±1.28^{a}	4.18±0.16^{a}	83.17±2.54^{c}
	AEHr (300mg/kg)	3.70±0.07^{cd}	140.00±2.58	104.17±1.64	24.50±1.4^{a}	3.18±0.16^{a}	78.83±1.22^{c}
Test Statistics	F-Ratio	39.14	0.044	0.659	6.784	119.3	127.1
	P-value	<0001****	0.9988 ^{ns}	0.6591^{ns}	0.0002***	<0.0001****	<0.0001****

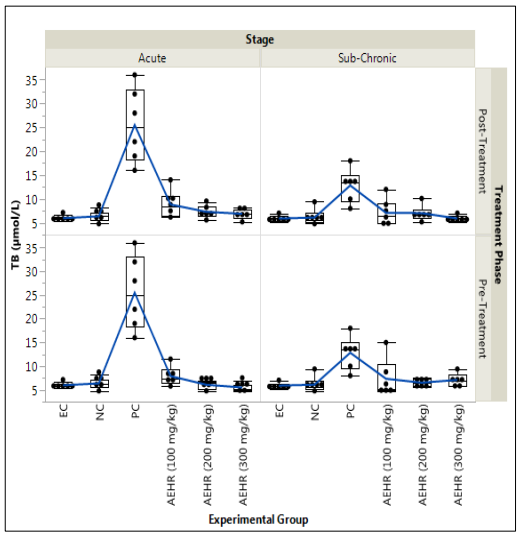
Abbreviations: SEM:Standard Error of Mean; K^{+}: Potassium; Na^{+} Sodium; Cl^{-}: Chloride; HCO_3^{-}: Bicarbonate.Experimental Groups: Extract Control (EC), Negative Control (NC), Positive Control (PC), Aqueous Extract of *Hypoestes rosea* at 100 mg/kg (AEHR (100 mg/kg)), AEHR (200 mg/kg), AEHR

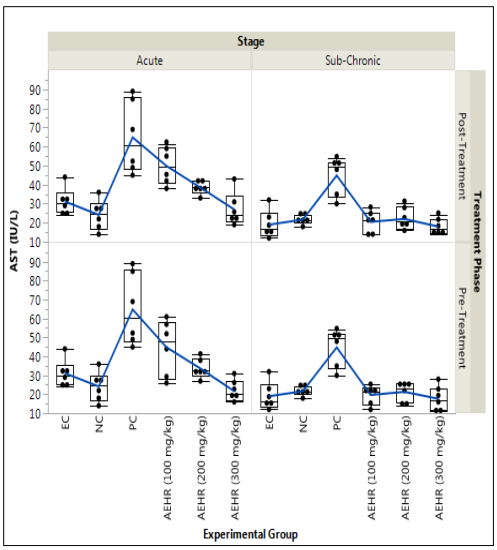
(300 mg/kg). Treatment Phases:Prophylactic (Pre-Treatment), Therapeutic (Post-Treatment.)Nfor each level mean=12.Within and across treatment phases by experimental groups, each parameter means ± SEM are not significantly different (p>0.05). Significance Level: ns=Not Significant (p>0.05).

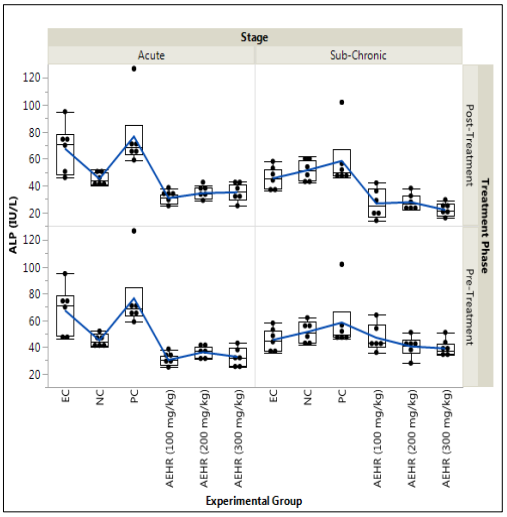
Table 4 : Sub-Chronic Effects of Various Concentrations of Aqueous Extract of *Hypoestes rosea* (AEHR) on Renal Function Parameters of Acetaminophen-Induced Albino Rats by Treatment Phase and Experimental Group.

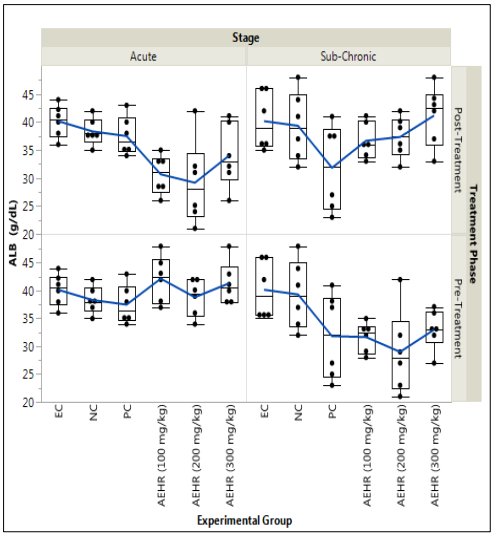
Treatment Phase	Experimental Group	K+ (mmol/L) Mean±SEM	Na+ (mmo/L) Mean±SEM	Cl - (mmol/L) Mean±SEM	HCO3- (mmol/L) Mean±SEM	Urea (mmol/L) Mean±SEM	Creatinine (mmol/L) Mean±SEM
(Prophylac-	EC	4.20±0.30^{a}	145.50±4.64	103.83±2.34	26.33±0.72^{a}	3.07±0.16^{e}	65.50±1.26^{ad}
tic	NC	4.35±0.30^{a}	143.33±1.59	103.83±2.21	24.50±0.56^{a}	4.25±0.15^{a}	72.67±2.89^{a}
Pre-Treat-	PC	6.77±0.17^{b}	138.00±1.24	101.17±1.08	21.33±1.05^{b}	11.95±0.26^{b}	195.50±4.18^{b}
ment)	AEHr (100mg/kg)	3.97±0.12^{a}	140.00±1.24	100.17±1.42	27.33±0.99^{a}	5.97±0.49^{ac}	84.33±3.16^{c}
	AEHr (200mg/kg)	3.57±0.84^{a}	138.83±1.62	105.33±2.42	26.50±0.96^{a}	4.27±0.17^{d}	77.33±3.08^{ac}
	AEHr (300mg/kg)	3.58±0.31^{a}	140.17±1.68	102.17±1.91	25.67±0.99^{a}	.3.23±0.15^{de}	70.17±1.82^{cd}
Test Statis-	F-Ratio	58.54	0.5956	0.8076	6.784	167	299
tics	*P-value*	<0.0001****	0.7037^{ns}	0.5534^{ns}	0.0002***	<0.0001****	<0.0001****
Therapeutic	EC	4.20±0.07^{a}	145.50±4.64	103.83±2.34	26.33±0.72^{a}	3.07±0.16^{e}	65.50±1.26^{ad}
(Post-Treat-	NC	4.35±0.30^{a}	143.33±1.59	103.83±2.22	24.50±0.56^{a}	4.25±0.15^{a}	72.67±2.89^{ae}
ment)	PC	6.77±0.17^{b}	138.00±1.24	101.17±1.08	21.33±1.05^{b}	11.95±0.26^{b}	195.50±4.18^{b}
	AEHr (100mg/kg)	3.72±0.12^{a}	138.33±1.12	104.00±1.73	25.00±0.63^{a}	5.59±0.46^{ac}	79.00± 2.46^{c}
	AEHr (200mg/kg)	3.40±0.06^{a}	139.50±2.31	102.17±1.83	22.17±1.20^{b}	4.05±0.15^{d}	74.50±2.87^{ce}
	AEHr (300mg/kg)	3.50±0.03^{a}	138.67±1.76	104.17±1.40	22.67±0.96^{b}	3.03±0.13^{de}	66.83±1.85^{ad}
Test Sta-	F-Ratio	66.68	0.08	0.77	6.902	186.5	342.70
tistics	*P-value*	<0.0001****	0.9953^{Ne}	0.5752 ^{ns}	0.0002***	<0.0001****	<0.0001

Box Plots Showing the Effects of Various Concentrations of Aqueous Extract of *Hypoestes rosea* (AE*Hr*) on Acetaminophen-Induced Toxicity in Albino Rats by Treatment Phase and Stage for some of the liver function parameters.



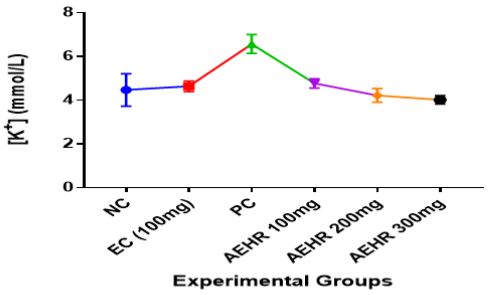




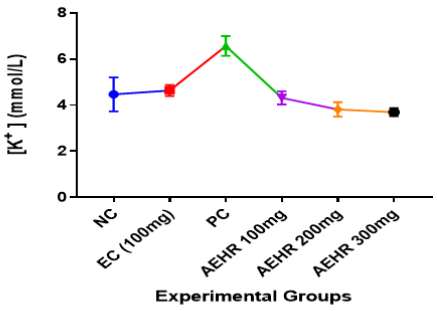


Box Plot of Potassium (K+) Showing the Effects of Various Concentrations of Aqueous Extract of *Hypoestes rosea* (AEHR) on Acetaminophen-Induced Toxicity in Albino Rats During (A) Acute pre-treatment Phase (B) Acute Post-treatment phase(C) Sub-chronic pre-treatment phase and(D) Sub-chronic Post-treatment phase.

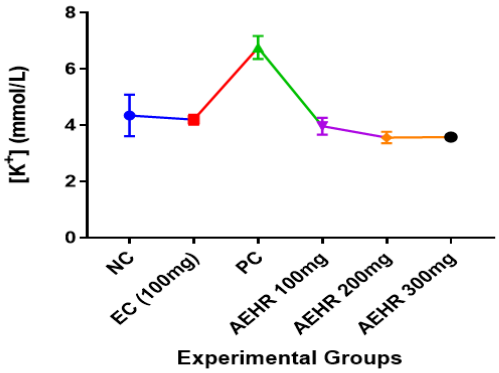
A



B



C



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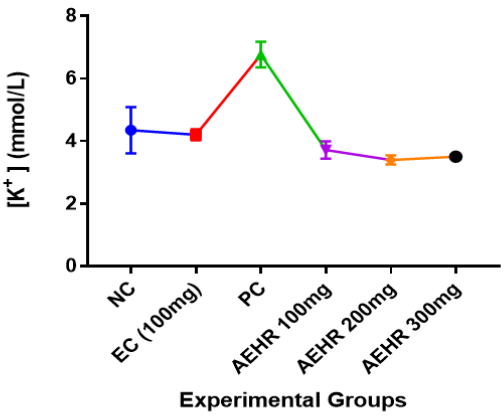

4. Conclusion

The results indicated that Hypoestes rosea has hepato-protective and nephroprotective properties, as evidenced by the liver and renal function tests. Hypoestes rosea leaves were accessible, safe and non-toxic at therapeutic doses. This research study, therefore, provides scientific evidence that Hypoestes rosea has hepatoprotective and nephroprotective potentials and further research studies in humans are highly encouraged.

Ethical Approval

Authors hereby declare that Principles of laboratory animal care (NIH publication No. 85- 23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee. All animal handling protocols were in accordance with institutional guidelines for laboratory animals. (Ethic Reference Number PM/27/08/2011/MAA (R) and OECD guidelines.

Competing Interests

The authors have declared that no competing interests exist.

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Case Report

Lymphedema in a patient with decompensated cirrhosis

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Abstract:

The lymphatic system is critical in body fluid homeostasis. Although lymphatic vascular expansion prevents the development of ascites and oedema in the early stages of liver cirrhosis, compensatory mechanisms cannot achieve this in the advanced stages due to lymphatic dysfunction. A 36-year-old male patient, who had been followed up for cryptogenic cirrhosis for 15 years, had been complaining of excessive swelling in his legs for the last 4 years. Excessive swelling in the legs was accompanied by skin rashes and ulcers, and the leg skin had an orange peel appearance characteristic of lymphedema. Bilateral lower extremity artery and venous system colour Doppler ultrasonography showed that the vascular structures of the right lower extremity arterial and venous system were open, and the flow rate, direction and spectrum were normal. The patient, who could not undergo liver transplantation due to organ limitations, died due to sepsis following lymphedema-induced wound infection. In conclusion, this case suggests that lymphedema should be considered in the presence of oedema in cases of decompensated cirrhosis, and the necessary conservative treatments should be applied.

Keywords: cirrhosis, lymphedema, lymphatic dysfunction, lymphatic system, oedema

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Introduction

Ascites and hepatic oedema are major complications observed in patients with decompensated cirrhosis and are associated with increased morbidity (1) and poor quality of life (2). The lymphatic vascular system plays a critical role in ascite formation. The lymphatic vascular system removes interstitial fluid from tissues in the body and returns it to the bloodstream. Failure of normal lymphatic function results in a build-up of interstitial fluid and can lead to lymphedema and ascites (3).

The liver is the largest lymph-producing organ, generating 25% to 50% of the lymph flowing through the thoracic duct. (4) Recent studies have suggested that the progression of liver disease causes structural and functional changes in both hepatic and extrahepatic lymphatic vessels. This suggests a possible link between lymphatic vessel changes and disease progression (5-6).

In this case report, we aim to present the lymphedema we encountered in a patient with liver cirrhosis.

Case Report

A 36-year-old male patient, who had been followed up for cryptogenic cirrhosis for 15 years, had been complaining of excessive swelling in his legs for the last 4 years. Excessive swelling in the legs was accompanied by skin rash and ulcers (*Figure 1*). His sister underwent a living donor liver transplantation due to cryptogenic liver cirrhosis. The patient had been

hospitalized twice before with the same complaint and had undergone debridement surgery at the plastic surgery department due to the wounds on his legs. In the last abdominal ultrasound examination, it was determined that the liver had a heterogeneous parenchymal echo, its contours were lobulated (chronic liver disease), the size of the spleen increased (16 cm), and there were massive ascites. Bilateral lower extremity artery and venous system colour Doppler ultrasonography showed that the vascular structures of the right lower extremity arterial and venous system were open, and the flow rate, direction and spectrum were normal. In the examination area, the subcutaneous tissue thickness is increased and edematous in the bilateral thigh and leg sections. *Figure 2* shows cirrhotic liver and massive ascites on dynamic liver tomography.

His laboratory values were creatinine 1.4 mg/dL, total bilirubin 11.95 mg/dL, direct bilirubin 7.19 mg/dL, prothrombin time INR 1.45, NA(Sodium):131 mmol/L, Albumine 1.4 G/DL, Cholesterol:52 mg/dL, Tg:96 mg/dL, VLDL 19.2. HBsAg and Anti-HCV were negative. MELD-Na and Child-Pugh scores 26 and 11, respectively.

Liver transplantation was planned due to decompensated cirrhosis. However, cadaveric or living donor liver transplantation could not be performed due to organ limitations. Cultures taken from the wounds on his legs grew Klebsiella pneumoniae and Pseudomonas aeruginosa bacteria. The patient did not respond to antibiotic treatments in the intensive care unit and died due to sepsis.

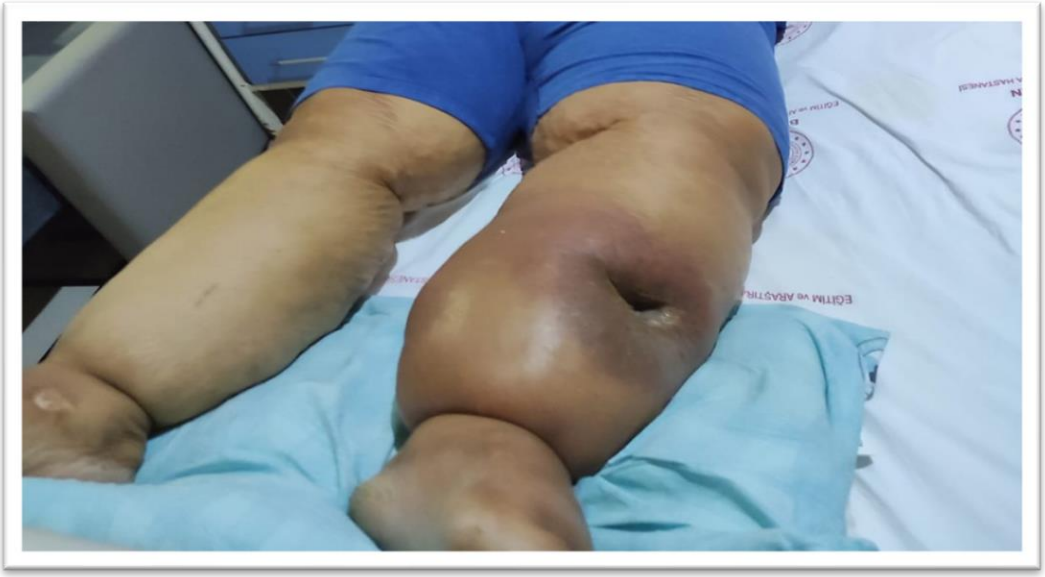

Figure 4 Excessive swelling in the legs was accompanied by skin rash and ulcers.

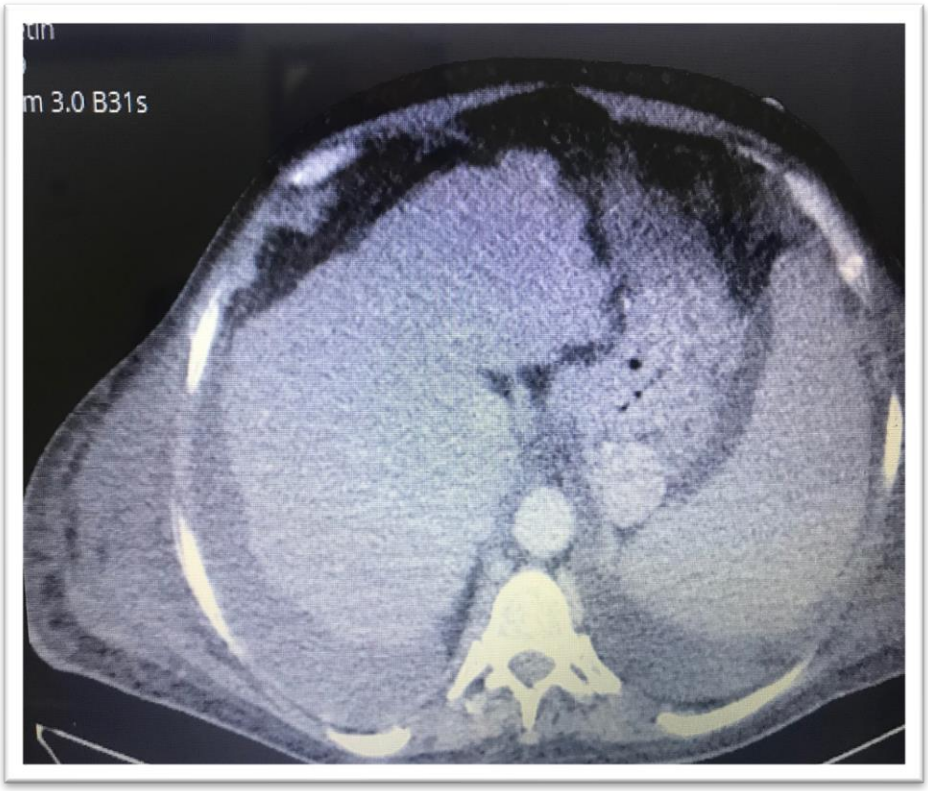

Figure 5 Dynamic Liver tomography shows cirrhotic liver and massive ascites.

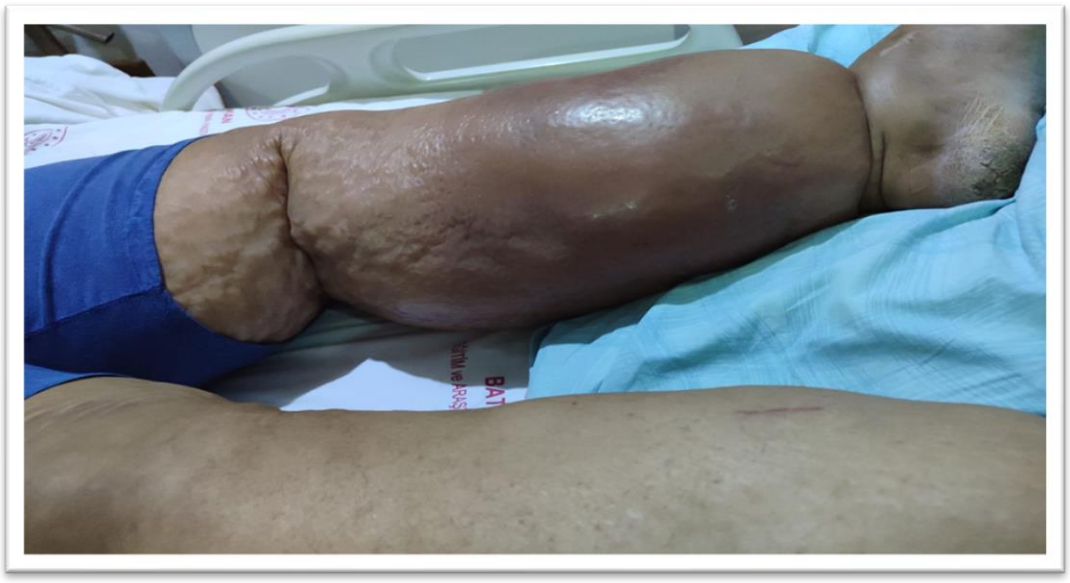

Figure 6 Typical lymphedema appearance on the left leg.

Discussion

Ascites and oedema are common in patients with decompensated cirrhosis. Since lymphedema is rare, it is generally considered as classical oedema in this patient group at first and is not brought to mind. In addition, lymphedema is generally considered an untreatable and resistant chronic problem. All of these may lead to diagnostic delays. To diagnose lymphedema, attention should be paid to the patient's risk factors and specific findings on physical examination (7). Peripheral lymphedema manifests itself physically as an orange peel appearance on the skin, as seen in *Figure 3*.

The lymphatic system is critical in body fluid homeostasis, adaptive immunity, and transport of lipids. In patients with liver cirrhosis, capillary filtration increases markedly due to an increase in hydrostatic pressure, resulting in increased lymph production. In the early stages, expansion of the lymphatic vascular system attempts to prevent fluid accumulation by returning fluid to the systemic circulation. However, with the progression of cirrhosis, lymphatic functions become compromised and, as a result, the lymphatic compensatory mechanism becomes overloaded, contributing to the development and eventual worsening of ascites and oedema (8). Additionally, there are studies reporting that the progression of liver disease is accompanied by changes in hepatic and extrahepatic lymphatic vessels (5-6). Although there are very few publications on lymphedema in patients with cirrhosis, the frequency of peripheral lymphedema in patients with cirrhosis and refractory ascites was reported as 33.5% in one study (9). The paucity of literature on lymphedema in patients with cirrhosis is probably due to the fact that patients are considered to have classical oedema and are less noticed, as well as the difficulties in the diagnosis and treatment of lymphedema.

In the treatment of lymphedema, intensive bandaging and lymphatic massage are essential, as well as the use of compression clothing. Surgical interventions may be required in cases that do not respond to conservative treatments (7). Our case had to undergo surgery twice due to deep ulcers. Patients with lymphedema are more prone to cellulite due to their deep fissures, stagnant lymph and weak immunity (9). Our case with decompensated cirrhosis also died due to sepsis following lymphedema-induced wound infection.

In conclusion, this case suggests that lymphedema should be considered in the presence of oedema in cases of decompensated cirrhosis, and the necessary conservative treatments should be applied.

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Case Report.

Renal Fornix Rupture Due to Acute Ureteral Obstruction

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Abstract: Background: Renal fornix rupture with fluid extravasation is a rare complication in cases of ureteral obstruction, which is usually caused by obstructive ureterolithiasis. The symptoms of renal fornix rupture are not very specific and can easily go unnoticed due to their underlying cause.

Case representation: The present article reports a case of a patient of a 70-year-old, male, who was diagnosed with a ruptured renal fornix due to acute ureteral obstruction, following clinical assessment and a non-contrast CT scan. The proposed course of action was the endoscopic placement of a double J ureteral catheter.

Conclusion: In the case described, the conservative treatment that was chosen by passing a double J catheter through the left ureter, for the patient proved to be an alternative to surgical treatment in the acute event, reducing the risk of possible complications from the operation. It was possible to conclude that although renal fornix rupture is a rare emergency with multiple etiologies, conservative treatment with urinary diversion using a double J ureteral stent was effective in solving the patient's acute condition.

Keywords: fornix rupture, ureterolithiasis, double J catheter, ureteral obstruction, clinical assessment

1. Introduction

Rupture of renal fornix with fluid extravasation is a rare complication in cases of ureteral obstruction, which is usually caused due to an obstructive, and therefore acute, ureterolithiasis. This condition may also be related to other pathologies, such as genitourinary tract neoplasms, the presence of a posterior urethral valve, the existence of retroperitoneal fibrosis, pregnancy, due to a large increase in intra-abdominal pressure (1, 2, 3, 4, 5) and benign prostatic hyperplasia, with few reports described (2).

The symptoms of renal phornix rupture are not very specific and can easily be disguised by its underlying cause, which usually presents as ureterolithiasis, i.e., it can present severe pain in the flank of the injured organ associated with nausea and vomiting (1,4,5). When its underlying cause is related to an infravesical obstruction, it can present with edema, leukocytosis, and even a bexigoma (2).

Its diagnosis can be made by associating the clinical examination with imaging tests, such as: excretory urography (1), USG, CT, which can identify perirenal fluid extravasation. In addition, it is important to emphasize that US is the test of choice in pregnant women due to the lack of exposure to radiation (1, 3, 4).

Emergency therapy for cases of fornix rupture due to ureterolithiasis consists of the passage of a double J catheter into the ureter of the injured kidney associated with antibiotic

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therapy, due to the infectious risk (1,2,3,4). In addition, other guidelines report that a tube can be placed for percutaneous nephrostomy to decompress the injured site (4).

Basede on this theme, the aim of this study is to highlight the relevance of the occurrence of a rare condition in urology, the fornix rupture and the type of treatment performed (conservative - passage of double J catheter) as an alternative to surgical treatment.

2. Materials and Methods

The database used to describe this report were: the analysis of medical records, evolution, laboratory tests and imaging tests carried out, which were applied to determine the respective diagnosis of the patient in question. In addition, previous studies of renal fornix rupture were used as a bibliographic reference, which were available in PubMed and Scielo.

3. Case Report

Patient D.G.B., male, 70 years old, was admitted to the emergency room with severe pain in the left flank, starting 7 hours ago. Associated with nausea and vomiting, he denied fever or other symptoms.

Past pathological history: coronary heart disease.

Commonly used medications: rosuvastatin and aspirin.

Allergies: denied.

Physical examination: Regular general condition, lucid and oriented in time and space, flushed, hydrated, anicteric, acyanotic and afebrile

Heart system: Regular rhythm in 2 beats, normal sounds, no audible murmurs

Respiratory system: breath sounds present, no adventitious sounds

Abdomen: flaccid and painful on palpation of the left flank.

Extremity: Peripheral pulses present and symmetrical, without cyanosis or edema

Laboratory tests: Hemoglobin: 14.9; Hematocrit: 43.9; Leukocytes: 10900 (neutrophils 87.9%, rods 2%); platelets 259,000; Creatinine: 0.75; Urea: 42; PCR: 0.5

Imaging test: (Image 1 and 2)

CT scan of the abdomen showed probable rupture of the phornix with the presence of perirenal fluid around the left kidney. No other changes.

Diagnostic hypothesis: The patient was admitted to hospital and instructed about the possible diagnosis of ureterolithiasis with probable fornix rupture and indication of double J catheter passage.

Evolution: In the operating room, a cystoscopy was performed with the passage of a double J catheter on the left, a procedure performed without intercurrences, in the post-operative period the patient presented slightly hematuric diuresis after passage of an indwelling urinary catheter, denying nausea, vomiting and other symptoms. Ceftriaxone was administered in-hospital for 2 days and at hospital discharge, cefuroxime was prescribed for 7 days and hydration. The patient was instructed to return for the removal of a double J catheter and for ultrasound of the kidneys and urinary tract to confirm the reabsorption of the perirenal fluid present around the left kidney.

On the return visit, ultrasound of the kidneys and urinary tract showed no abnormalities. The removal of the double J catheter was scheduled. The patient had a good clinical evolution after the procedure.

Figure 1 *Figure 2.*

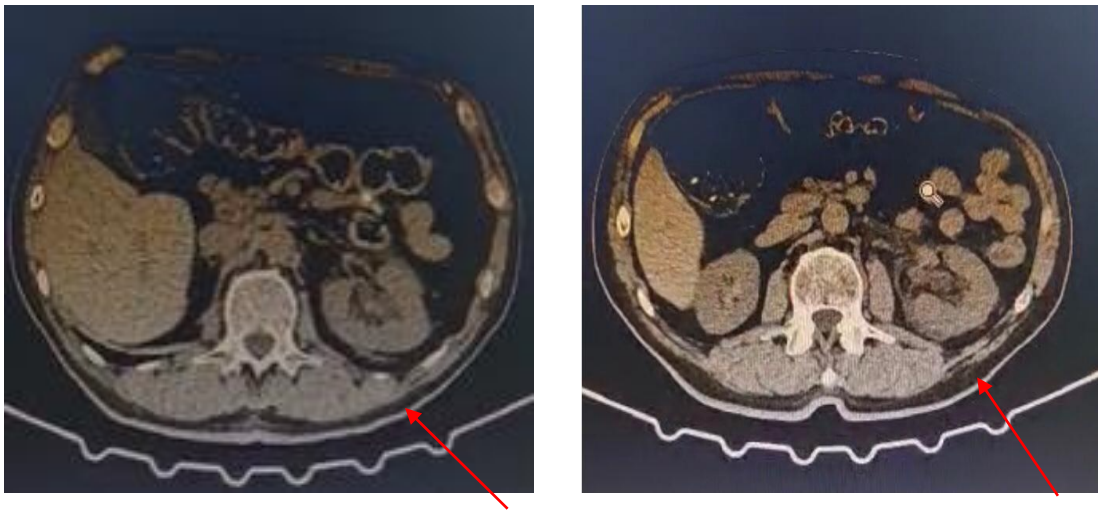

Figure 1 and 2: The arrow shows the renal fornix rupture.

4. Discussion

Rupture of renal fornix with fluid extravasation is a rare case within the urological entity, and may or may not be of traumatic origin (3). According to a study produced by Ercil et al., in 43 patients diagnosed with fornix rupture, 77.4% were caused due to pre-existing renal lithiasis, in 4 different cases (9.3%) there was no underlying diagnostic cause for this outcome (3, 6 and 7). The obstruction, associated with the increase in the intraluminal pressure of the ureter, can cause the rupture of the collecting system and consequently, a mechanism explained by Laplace's law, the tensile stress transmitted through a dilated collecting system increases with size, thus causing fornix rupture in a more dilated system, an increase in pressure that exceeds the tensile strength of the fornix tissues leads to interruption and extravasation of urine. (5,8). Such as what occurred in the present case report.

The clinical picture presented may be variable, such as the presence of pain in the flank of the injured kidney, nausea, vomiting, or even characterized as an acute abdomen. Therefore, clinical presentations such as pyelonephritis, appendicitis, duodenal ulcer and symptomatic cholelithiasis can be identified based on these symptoms, in addition to being differential diagnoses in this case(7).

From the point of view of diagnostic imaging, ultrasonography can identify hydronephrosis, the presence of collections, or the presence of stones. However, the reference test is a computed tomography scan with delayed time acquisition, which can accurately show the contrast extravasation and the exact site of the rupture (8,9). The most common form, approximately 75% of cases, is distal rupture, due to the majority of stones being located below the sacroiliac vessels (i.e., distal ureter and UVJ) and distal stones were significantly smaller than the proximal stones observed by the systematic review of 108 cases by Gershman B.et. al (10).

The emergency treatment described in the literature consists of a urinary diversion by double ureteral stent J or percutaneous nephrostomy, with the treatment of the underlying cause, which should be performed after resolution of the acute episode, as was done in the case described in this article(3,8,11). If left untreated, this formed urinoma can lead to the

formation of perirenal abscess, sepsis, retroperitoneal fibrosis, loss of function, and even death, with the prognosis varying according to the patient's underlying pathologies, renal injury, rupture site, and presence of infection (3,10 and 11). Thus, justifying the use of antibiotic therapy in the postoperative period, which evolved favorably.

5. Conclusions

Renal fornix rupture is a rare emergency of multiple etiologies. In this way, studies that lead to the detailing of patients affected by this disease in other institutions can contribute to a positive evolution in the quality of hospital care. In addition, it can be concluded that conservative treatment with urinary bypass in a double ureteral J stent is effective and has good results.

Moreover, due to the fact that there are few cases reported and discussed in the literature, it can be concluded that this study was extremely important, as it could help, in different way, future conduct when urologists are faced with rare case of renal fornix rupture.

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Research Article

Haemoglobin Variants, ABO/Rh Blood Groups and their Associations with Levels of Malaria Parasitaemia amongst Infected Subjects at Rivers State University, Port Harcourt, Nigeria

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Abstract: The aim of the study was to associate haemoglobin variants, ABO/Rh blood groups with levels of malaria parasitaemia amongst infected subjects at Rivers State University, Port Harcourt, Nigeria. ABO/Rh D blood groups were analyzed using monoclonal antisera, and haemoglobin electrophoresis was analyzed using the alkaline cellulose acetate electrophoresis method, while malaria parasites were identified by microscopic examination of stained blood films. Graph Pad Prism version 8.0 was used to statistically analyze odd ratios, confidence intervals, likelihood ratios and relative risks. All 147 subjects (87 females, 60 males) were positive for malaria (*Plasmodium falciparum*). For 3+ *falciparum* malaria, the order of infection for haemoglobin genotype was AA > AS/SS; ABO blood group was B > A > O > AB; Rh blood group was Rh D+ > Rh D-; gender was females > males at $p > 0.05$. At $p > 0.05$, for 2+ *falciparum* malaria: haemoglobin genotype was SS >AA > AS; ABO blood group was B > A > O > AB; Rh blood group was Rh D- > Rh D+; and gender was females > Males. At $p > 0.05$, for 1+ *falciparum* malaria infection: haemoglobin genotype was AS >AA > SS; ABO blood group was AB > O > A > B; Rh blood group was Rh D+ > Rh D-; and gender was males > females. Conclusively, 3+ *Plasmodium falciparum* malaria infection is common amongst individuals with: AA haemoglobin genotype, blood group B, Rh D+, and females; 2+ *P. falciparum* infection is common amongst individuals with: haemoglobin genotype AA, blood group B, Rh D-, and females; while 1+ *P. falciparum* malaria infection is common amongst individuals with: AS haemogobin genotype, blood group AB, Rh D+, and amongst males than females.

Keywords: Malaria Parasite; Haemoglobin Electrophoresis; ABO Blood group; Rh D Blood Group; falciparum malaria.

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1. Introduction

Blood is a fluid tissue that transports nutrients and oxygen to all parts of the body while also removing waste (carbon dioxide) from the body. It is composed of red blood cells, white blood cells and platelets suspended in plasma, (1); the red blood cell contain haemoglobin that malaria parasites feed on.

Blood group antigens are present on the surfaces red blood cell (RBC) membrane and their specificity can be determined by a number of genes that can be allelic or extremely closely linked on the same chromosome. The blood type describes the pattern of response to testing antisera and can be identified serologically in the laboratory based on antigen-antibody reactions (2).

The International Society of Blood Transfusion (ISBT) has a list of 33 blood group systems that represent more than 300 antigens (3; 4). The majority of them have been sequenced and cloned. ABO continues to be the most important of the 33 systems for transfusion and transplantation since anybody older than 6 months has clinically significant levels of anti-A and/or anti-B antibodies in their serum. While blood group O lacks the A/B antigen but does carry both of its antibodies in serum, blood group A carries an antibody against blood group B and vice versa (2).

The Rh system is the second most significant blood group system after ABO (5). Many years ago, the Rh blood type system was initially described. After giving birth to a stillborn child with erythroblastosis fetalis, a mother who had blood transfusions from her husband experienced a severe transfusion reaction (6). Later on, Landsteiner and Wiener (7), discovered that 85% of human RBC samples were agglutinated by sera from rabbits (and later guinea pigs) immunized with Macaca mulatta RBCs (Macacus Rhesus in the original publication). At first, it was believed that the antibodies from animals and humans had found Rh on the surface of human and Rhesus RBCs. This was not the case, as was quickly realized (8).

Haemoglobin is necessary for the transport of oxygen throughout the body (9;10). It has the ability to combine with oxygen in a reversible manner. Due to the four haem groups' enhanced interaction in an environment with high oxygen tension, the haemoglobin molecule rapidly saturates with oxygen to create oxy-haemoglobin (11). The haemoglobin that is found in red blood cells is what malaria parasites (*Plasmodium falciparum*) feeds on.

Normal haemoglobin has a valine in place of glutamic acid in position six of the beta chain of the globin molecule, which distinguishes sickle cell haemoglobin (HbS) from normal haemoglobin (HbA). Erythrocytes with sickle cell haemoglobin develop sickle-shaped cells instead of the usual round, biconcave disc shape when oxygen levels are decreased. Anaemia is nearly universally experienced by sickle cell homozygotes (HbS/HbS). The HbA/HbS sickle cell heterozygote possesses malaria parasitemia resistance and is only mildly anaemic (12).

The haemoglobin variants present in the blood, which directly or indirectly influence the amount of haemoglobin, are important for predicting the blood's capacity to deliver oxygen to the body's tissues and the likelihood that the person will have sickle cell anaemia (13), and moreso, the amount of haemoglobin available for malaria parasite to feed on.

Malaria is a parasite-borne illness spread by the Anopheles species of mosquitoes and caused by *Plasmodium* parasites. The five *Plasmodium species* which affect humans include *P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi*. The two most prevalent species are *P. falciparum* and *P. vivax,* with *P. falciparum* being more prevalent in tropical and subtropical regions, particularly in Africa (and Nigeria, where the study was conducted), and *P. vivax* being more prevalent in Asia, Latin America, and portions of Africa (14; 15; 16).

A study has indicated a correlation between the ABO blood group and the resistance, susceptibility, and severity of malaria infection caused by *P. falciparum*. Blood group "O" is thought to provide protection against complex cases of *falciparum* malaria, while blood group "A" has been proven to be particularly susceptible to the disease (17).

The sickle cell mutation is related to malaria because the malaria parasite causes hypoxia when it infects a red blood cell. When such blood cells sickle in individuals with the AS genotype, the body's immune system macrophage cells remove them, thereby reducing the risk of infection (18).

Sickle cell trait carriers are less resistant to mild occurrences of malaria but more resistant to severe episodes. The acquired immunity that both AA and AS individuals get after multiple exposures to the disease is not the same as the mechanism by which carriers are protected from malaria (19).

2. Materials and Methods

2.1 Study Design

This study was a cross-sectional study carried out among malaria-infected subjects attending the Rivers State University Medical Centre, Port Harcourt.

2.2 Study Area

Rivers State University, formerly called Rivers State University of Science and Technology is a university located in the Diobu area of Nkpolu-Oroworokwu, Port Harcourt, Rivers State in South–South, Nigeria. All participants were recruited from Rivers State University, Port Harcourt. Rivers State University is located on latitude 4.7958^0 N and longitude 7.0246^0 E. The analysis was carried out at Prof. Nimi Briggs Hospital (the Medical Center), Rivers State University. Port Harcourt, the capital of Rivers State is located on latitude 4.75^0 N and longitude 7.00^0 E and lies along Bonny River in the Niger Delta.

2.3 Study Population

Based on convenient sampling, a total of one hundred and forty-seven (147) human subjects consisting of sixty (60) males and eighty-seven (87) females, confirmed positive for *falciparum* malaria, attending the Rivers State University Medical Centre, Port Harcourt, Rivers State were recruited for the study. The study subjects were adults varying between 16-60 years of age.

2.4 Sample Collection

After pre-test counselling and explanations, venous blood collection was drawn from the antecubital fossa of the subjects with the use of vacutainer as described by Ochei and Kolhatkar (11). Three (3.0) ml of venous blood was collected into a glass vacutainer sample bottle that contains 0.5ml of 1.2mg/ml of dipotassium ethylene diamine tetra-acetic acid (EDTA). All blood samples were analyzed within 24 hours of collection.

2.5 Methodology

2.5.1 Determination of ABO and Rh D Blood Group Using Atlas Monoclonal Antisera.

Principle: The presence or absence of A, B on human red blood cells can be determined by testing the red blood cells with the respective antisera, specifically Anti-A, Anti-B, Anti-AB. The procedure is based on the principle of agglutination (20).

Procedure: For ABO blood group, a drop of anti-A, anti-B, and anti-AB (Atlas Medical), each was placed in a clean tube labeled A, B, AB and O. A drop of red cell was added to the part labeled A, B, AB and O and anti-A, anti-B, anti-AB was dropped in the part labeled A, B, AB and O, the mixture was centrifuged for about 30 seconds at 3500rpm and thereafter observed for agglutination. Presence of agglutination indicated a positive result while absence of agglutination indicates a negative result. Same procedure was applied for Rh blood group, a drop of anti-D (Atlas Medical) was placed in a clean glass tube labeled D. A drop of red cell was added to the tube labeled D, the mixture was centrifuged at 3500rpm for 30 seconds and thereafter observe for agglutination. Presence of agglutination indicated a positive result while absence of agglutination indicates a negative result (20).

2.5.2 Determination of Haemoglobin Genotype

Principle: In an alkaline buffer at pH 8.4-8.6 using a cellulose acetate membrane, haemoglobin variants separate at different rates due to differences in their surface electrical charge as determined by their amino acid structure (20).

Procedure for Haemoglobin Genotype: The red blood cells were haemolyzed with the haemolyzing reagent and the electrophoresis tank was prepared by placing equal amount of Tris buffer in the different compartments. The chamber wicks were wetted in the buffer

and placed one across the bridge ensuring there is contact with the buffer. Thereafter, the cellulose acetate paper was soaked into a reserve buffer for 5 minutes. With the aid of an applicator stick, the haemolyzed sample was loaded to the blotting paper (cellulose acetate paper). The cellulose acetate paper was placed across the bridge and power was turned on for electrophoresis to take place at 350V for 25 minutes. After 25 minutes of electrophoresis, the cellulose acetate paper was transferred to the staining reagent to fix for 5 minutes. Excess stain was removed by washing for 5 minutes in acetic acid and 10 minutes in the remaining de-staining reagent. The membrane was labeled and results were interpreted (20).

Interpretation of Results: The results of a haemoglobin electrophoresis test are interpreted by comparing the pattern of bands on the gel or paper strip to a known pattern. The known pattern will show the different types of haemoglobin that were present in the blood sample.

2.5.3 Identification of Malaria Parasite

Principle of Giemsa Stain: Giemsa solution is composed of eosin and methylene blue (azure). The eosin component stains the parasite nucleus red, while the methylene blue component stains the cytoplasm blue (20).

Procedure for Thick Film Preparation: Two drops of blood were placed on a clean glass slide and the blood was mixed with the head of a pipette in circular motion over an area about two centimeter in diameter. The blood film was allowed to air-dry at room temperature (20).

Procedure for Staining of Thick Film: 1 in 30 dilution of Giemsa's stain was made by mixing 1ml of the stain in 29ml of buffered water, the film was dried for some hours. The film was covered with diluted Giemsa's stain for 30 minutes, and washed in buffered water at pH of 7.2. The film was dried in a vertical position, and later examined microscopically using oil immersion objective (100x) (20).

Interpretation of Results: 1–10/100 HPF = 1+**;** 11–20/100 HPF = 2+**;** 1–10/10 HPF = 3+**;** 11–20/10 HPF = 4+

2.6 Statistical Analysis

Data collected were statistically analyzed for percentage distribution, odd ratio, relative risk, confidence interval and likelihood ratio using Graph Pad Prism version 8.0. Data are represented in Tables.

3. Results

This section can be divided into multiple sub-sections to ensure that the results are presented in the best possible format. We strongly recommend using tables, and figures, in this part of the article.

3.1: Demographic Details of Studied Population

A total of 147 *falciparum* malaria infected subjects participated in the study. Males were sixty (60) while females were eighty-seven (87).

3.2: Frequency and Percentage Distribution of Malaria based on Levels of Parasitemia

The frequency and percentage distribution of *falciparum* malaria based on levels of parasitemia were analyzed and recorded. Details are shown in Table 1.

Table 1. Frequency and Percentage Distribution of *falciparum* Malaria based on Levels of Parasitemia

Parameters	Frequency (f)	Percentage (%)
1+ *falciparum* malaria	98	66.7%
2+ *falciparum* malaria	45	30.6%
3+ *falciparum* malaria	4	2.7%

3.3: Frequency Occurrence and Percentage Distribution of Malaria Infection in the Studied Population based on gender

The frequency and percentage distributions of malaria infection based on gender were analyzed and recorded. Details are shown in Table 2.

Table 2. Frequency Occurrence and Percentage Distribution of Malaria Infection in the Studied Population based on gender

Parameters	Total Population (N)	Frequency	Percentage (%)
1+ *falciparum* malaria	98	M = 42	M = 28.6
		F = 56	F = 38.1
2+ *falciparum* malaria	45	M = 17	M = 11.6
		F = 28	F = 19.0
3+ *falciparum* malaria	4	M = 1	M = 0.7
		F = 3	F = 2.0

3.4: Comparison of Odds Ratios, Relative Risks and Likelihood Ratios of 3+ Plasmodium falciparum Malaria based on Genotype, Blood Groups and Gender Differences

Based on their odds the likelihood of having 3+ infection with Plasmodium falciparum malaria for the studied variables at $p > 0.05$, were in the order of: Genotype – AA > AS/SS with odds of infinity and 0.00 respectively; ABO blood group – B > A > O > AB with odds of 2.16 > 0.79 > 0.24 > 0.00 respectively; Rh blood group – Rh D+ > Rh D- with odds of infinity > 0.00 respectively; and Gender – Female > Male with odds of 2.05 > 0.48 respectively. Details are shown in Table 3.

Table 3. Odds Ratios, Relative Risks and Likelihood Ratios of being infected with 3+ *Plasmodium falciparum* Malaria based on Genotype, Blood Group and Gender Differences

Variables	Odds Ratio	Relative Risk	Likelihood Ratio	p-value
Genotype AA	Infinity	Infinity	1.26	0.5837 ^{NS}
A				

	CI 0.279 to Infinity	CI 0.242 to Infinity		
Genotype AS	0.00 CI 0.279 to Infinity	0.00 CI 0.242 to Infinity	0.00	>0.9999^{NS}
Genotype SS	0.00 CI 0.000 to 88.79	0.00 CI 0.000 to 36.75	0.00	>0.9999^{NS}
Blood Group A	0.79 CI 0.119 to 5.311	0.00 CI 0.000 to 36.75	0.00	>0.9999^{NS}
Blood Group B	2.16 CI 0.159 to 14.93	2.11 CI 0.305 to 13.81	1.87	0.4467^{NS}
Blood Group AB	0.00 CI 0.000 to 337.5	0.00 CI 0.000 to 49.43	0.43	>0.9999^{NS}
Blood Group O	0.24 CI 0.018 to 1.66	0.25 CI 0.036 to 1.70	0.00	0.3142^{NS}
Blood Group Rh D+	Infinity CI 0.022 to Infinity	infinity CI 0.048 to Infinity	1.03	>0.9999^{NS}
Blood Group Rh D-	0.00 CI 0.000 to 1.355	0.00 CI 0.000 to 1.193	0.00	0.2208^{NS}
Females	0.00 CI 0.299 to 27.10	0.00 CI 0.297 to 13.98	1,26	0.6487^{NS}
Males	0.00 CI 0.036 to 3.339	0.00 CI 0.071 to 3.358	0.61	0.6487^{NS}

3.5: Comparison of Odds Ratios, Relative Risks and Likelihood Ratios of 2+ Plasmodium falciparum Malaria based on Genotype, Blood Groups and Gender Differences

Based on their odds, the likelihood of having 2+ infection with Plasmodium falciparum malaria for the studied variables at $p > 0.05$, were in the order of: Genotype – SS >AA > AS with odds of 1.64 > 1.21 > 0.76 respectively; ABO blood group – B > A > O > AB with odds of 1.38 > 1.16 > 0.75 > 0.00 respectively; Rh blood group – Rh D- > Rh D+ with odds of 1.34 > 0.74 respectively; and Gender – Female > Male with odds of 1.24 > 0.80 respectively. Details are shown in Table 4.

Table 4. Odds Ratios, Relative Risks and Likelihood Ratios of being infected with 2+ *Plasmodium falciparum* Malaria based on Genotype, Blood Group and Gender Differences

Variables	Odds Ratio	Relative Risk	Likelihood Ratio	p-value
Genotype AA	1.21 CI 0.519 to 2.712	1.12 CI 0.617 to 2.319	1.03	0.8322^{NS}
Genotype AS	0.76 CI 0.294 to 1.893	0.81 CI 0.389 to 1.575	0.80	0.6651^{NS}
Genotype SS	1.64 CI 0.111 to 14.35	1.43 CI 0.260 to 3.665	1.63	0.5539^{NS}
Blood Group A	1.16 CI 0.568 to 2.414	1.12 CI 0.629 to 1.906	1.11	0.7039^{NS}
Blood Group B	1.38 CI 0.554 to 3.283	1.27 CI 0.664 to 2.257	1.30	0.4932^{NS}
Blood Group AB	0.00 CI 0.000 to 0030	0.00 CI 0.000 to 3.600	0.00	>0.9999^{NS}
Blood Group O	0.75 CI 0.396 to 1.452	0.81 CI 0.487 to 1.345	0.88	0.4935^{NS}
Blood Group Rh D+	0.74 CI 0.150 to 3.839	0.80 CI 0.333 to 2.841	0.98	0.6628^{NS}
Blood Group Rh D-	0.00 CI 0.000 to 1.355	0.00 CI 0.000 to 1.193	0.00	0.2208^{NS}
Females	1.34 CI 0.260 to 6.640	1.25 CI 0.352 to 2.999	1.33	0.6628^{NS}
Males	0.80 CI 0.411 to 1.57	0.85 CI 0.491 to 1.427	0.87	0.6040^{NS}

3.6: Comparison of Odds Ratios, Relative Risks and Likelihood Ratios of 1+ Plasmodium falciparum Malaria based on Genotype, Blood Groups and Gender Differences

Based on their odds the likelihood of having 1+ infection with *Plasmodium falciparum* malaria for the studied variables at $p > 0.05$, were in the order of: Genotype – AS >AA > SS with odds of 1.13 > 0.84 > 0.76 respectively; ABO blood group – AB > O > A > B with odds of 1.54 > 1.14 > 0.87 > 0.84 respectively; Rh blood group – Rh D+ > Rh D- with odds of 1.09 > 0.92 respectively; and Gender – Male > Female with odds of 1.14 > 0.87 respectively. Details are shown in Table 5.

Table 5. Odds Ratios, Relative Risks and Likelihood Ratios of being infected with 1+ *Plasmodium falciparum* Malaria based on Genotype, Blood Group and Gender Differences

Variables	Odds Ratio	Relative Risk	Likelihood Ratio	p-value
Genotype AA	0.84 CI 0.454 to 1.563	0.90 CI 0.650 to 1.325	0.96	0.6384^{NS}
Genotype AS	1.13 CI 0.591 to 2.095	1.08 CI 0.728 to 1.520	1.11	0.7469^{NS}
Genotype SS	0.76 CI 0.052 to 6.638	0.84 CI 0.154 to 2.061	0.76	>0.9999^{NS}
Blood Group A	0.87 CI 0.489 to 1.554	0.92 CI 0.625 to 1.300	0.90	0.7644^{NS}
Blood Group B	0.92 CI 0.625 to 1.300	0.90 CI 0.546 to 1.364	0.86	0.7149^{NS}
Blood Group AB	1.54 CI 0.080 to 29.36	1.27 CI 0.238 to 2.396	1.53	>0.9999^{NS}
Blood Group O	1.14 CI 0.707 to 1.980	1.11 CI 0.814 to 1.545	1.07	0.5965^{NS}
Blood Group Rh D+	1.09 CI 0.280 to 4.202	1.05 CI 0.552 to 2.921	1.00	>0.9999^{NS}
Blood Group Rh D-	0.92 CI 0.238 to 3.560	0.95 CI 0.342 to 1.810	0.92	>0.9999^{NS}
Females	0.87	0.92	0.95	0.6931^{NS}

	CI 0.522 to 1.479	CI 0.680 to 1.264		
Males	1.14 CI 0.676 to 1.914	1.08 CI 0.791 to 1.469	1.08	0.6931^{NS}

4. Discussion

The study revealed that 2.7% of the studied subjects were infected with 3+ *falciparum* malaria, subjects infected with 2+ was 30.6%, and 66.7% had 1+ *falciparum* malaria infection. The reason for having more of 1+ infection may be as a result of anti-malaria medication that have reduced the parasite load.

Based on the relationship of ABO/Rh blood groups and haemoglobin genotypes with malaria parasitemia, odd ratios find its usefulness in comparing the relative odds for the occurrence of the possible outcome of a disorder or disease (in this case, malaria). The odd ratio establishes the risk factor for malaria parasitaemia in relation to the presence of the different blood group antigens, haemoglobin genotypes and gender. An odd ratio (OR = 1) indicates that the result, malaria parasitaemia, will not be impacted by the presence of that antigen and haemoglobin genotype. An odd ratio (OR > 1) indicates that a blood group antigen's and haemoglobin genotype's presence is linked to an increased level of malaria parasitaemia. A blood group antigen and haemoglobin genotype with an odd ratio (OR < 1) suggests that having it is linked to a lower level of malaria parasitaemia. The likelihood ratio gives the usefulness of the blood group outcomes in ascertaining which blood group and genotype is more likely prone to be at risk of malaria. Confidence interval finds usefulness in estimating the precision of odd ratios; a large confidence interval is indicative of a low level of precision of the odd ratios, while a small confidence interval is indicative of a higher precision. So, the combination of odd ratios and confidence interval will give a better interpretation of the degree of malaria parasitaemia risk.

For haemoglobin variants consideration, the risk of being infected with 3+ *plasmodium falciparum* malaria, indicated that individuals with AA genotype were more infected with 3+ *Plasmodium falciparum* malaria than individuals with the AS haemoglobin genotype. The study carried out by Bougouma *et al.* (21) revealed AS genotype was associated with lower incidence of clinical malaria relative to AA genotype among children aged 2–3 years, and their findings are not in deviation from the findings in this study, though with younger subjects. Similar to AS, individuals with the SS haemoglobin genotype have a very low chance of infection. For ABO blood group as a factor, considering 3+ *plasmodium falciparum* malaria, the order of infection was: B > A > O > AB, however considering the fact that the p-value and confidence intervals were not statistically significant, this finding calls for a more robust research. The finding from this study is contradictory to a study presented by Zerihun *et al.* (22) which indicated that *P. falciparum* infection showed significant association with blood types (P<0.05) and the chance of having *P. falciparum* infection in patients with blood groups A, B and AB was 2.5, 2.5 and 3.3 times more than individuals having blood O phenotypes, respectively. The variation observed could arise from variations in gene frequencies. For Rh D factor, its presence (Rh D+) indicated a high infection rate as seen from the study. However, considering the number of Rh D- subjects (3 subjects), the comparison is not robust enough to draw a statistical conclusion; this is in agreement with a research carried out by Rattanapan *et al.* (23) where they reported no link between the Rh D blood group and malaria. Based on gender, the females may likely be infected with 3+ *falciparum* malaria than males, but considering the confidence interval and p-value which is >1 and >0.05 respectively, gender may not be considered as a risk factor for malaria in the studied population.

Consideration statistical outcomes for being infected with 2+ *plasmodium falciparum* malaria, the study revealed that subjects with the AA haemoglobin genotype had slightly increased numbers. Subjects with the AS genotype recorded a slightly decreased outcome in terms of number of infections, but again, this difference is not statistically significant. The

odd ratios (OR) for the blood groups under consideration of associating them as a risk factor of being infected with 2+ *plasmodium falciparum* malaria, indicated that none of the blood groups (A, B, AB, O) showed strong association with the risk of 2+ *falciparum* malaria infection, however, the infection trend indicated (B > A > O > AB) but with p-values and confidence intervals that are not statistically significant. Both Rh D+ and Rh D- individuals do not show a significant difference in the risk of infection with 2+ malaria. Based on gender, there is difference in numbers; the trend indicates that the female gender was more infected with *falciparum* malaria than their male counterpart; however, considering the outcomes of p-values and confidence intervals, this may not be considered clinically relevant in the epidemiology of the disease.

For 1+ *plasmodium falciparum* malaria, the study revealed that subjects with the AA genotype have a slightly decreased outcome in terms of being infected with 1+ *Plasmodium falciparum* malaria than subjects who are of the AS. Individuals with AS haemoglobin variants were more compared to other variants – this may be as a result of the reduced ability of *Plasmodium falciparum* parasites to grow and multiply in HbAS red blood cells, and also because they are less likely to fall ill compared to AA individual; thus, they do not take malaria prophylaxis as often as subjects who are AA, who whenever they are attacked, their response to *falciparum* malaria seems to be more severe than AS individuals, and the prophylaxis likely to have reduced the parasite load. For the blood groups under consideration, none of the blood groups (A, B, AB, O) indicated a strong association with the risk of 1+ *falciparum* malaria infection. The differences in odds, risk, and likelihood ratios were not statistically significant; the confidence intervals were large; and based on these outcomes, there are no association; and this is also applicable to gender disparity (there is no association found between gender and malaria infection). However, a research conducted by Okiring *et al.* (24) indicates a higher likelihood of females contracting malaria compared to males. Possible reasons for the difference in this study to that of theirs could be as environmental factors and variations in sample size.

5. Conclusions

Conclusively, 3+ *Plasmodium falciparum* malaria infection is common amongst individuals with AA haemoglobin genotype, blood group B, Rh D+ and females; 2+ *P. falciparum* infection is common amongst individuals with haemoglobin genotype AA, blood group B, Rh D- and females; while 1+ *P. falciparum* malaria infection is common amongst individuals with AS haemogobin genotype, blood group AB and Rh D+, and amongst males than females.

6. Recommendation

We recommend a larger sample size be considered for further studies, and the use of molecular techniques for malaria diagnosis and quantitation.

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Informed Consent Statement: "Informed consent was obtained from all subjects involved in the study.

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Case Report

Mucormycosis And Hemophagocytosis Syndrome in A Patient Following Acute Myeloid Leukemia

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Abstract:

Acute Myeloid Leukemia (AML) is a malignant disease that affects the bone marrow and may affect red blood cells, white blood cells(myeloblasts), and platelets. Some cases of disease may be asymptomatic and can be diagnosed from random blood tests. AML mostly affects cells that are not fully developed, causing these cells to fail to perform their normal functions. If this disease is left untreated, it gets worse quickly and can be fatal. Genetic factors may cause the development of AML, but the exact cause is not known. There are environmental factors in AML etiology (eg, chemicals, radiation, tobacco, chemotherapy), in some patients, AML may occur due to clonal hematopoiesis manifest as a myelodysplastic syndrome, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, aplastic anemia and more. Here we present a case report of 59 years old male patient presenting to the clinic with malaise and referred to haematology department due to pancytopenia. However, further investigations confirmed AML.

Keywords: Acute Myeloid Leukemia (AML),Mucormycosis, Hemophagocytic lymphohistiocytosis (HLH), case report, mucormycosis, hemophagocytosis

Introduction

Acute Myeloid Leukemia (AML) is a malignant disease that affects the bone marrow and may affect red blood cells, white blood cells(myeloblasts), and platelets. Some cases of disease may be asymptomatic and can be diagnosed from random blood tests. AML mostly affects cells that are not fully developed, causing these cells to fail to perform their normal functions. If this disease is left untreated, it gets worsely quickly and can be fatal. Genetic factors may cause the development of AML, but the exact cause is not known. There are environmental factors in AML etiology (eg,chemicals, radiation, tobacco, chemotherapy), in some patients, AML may occur due to clonal hematopoiesis manifest as a myelodysplastic syndrome, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, aplastic anemia etc.

Clinical presentation: anemia (eg, shortness of breath, weakness, dyspnea), thrombocytopenia (excess bleeding or bruising), and neutropenia (fever, infections),hepatomegaly, splenomegaly are common but lymphadenopathy is rare.

Mucormycosis usually occurs in immunosuppressed hematology patients and is fatal. Since this disease does not have a specific clinical method, it is often not diagnosed. Mucormycosis is caused by opportunistic fungal pathogens and is more common in immunosuppressed hematology patients receiving chemotherapy or in patients who have undergone bone marrow transfer. These microorganisms are found everywhere in nature and in decaying

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plants and soil. All people encounter this fungus every day. The only reason why this disease is rare in humans is the immune system

RISK FACTORS:

- Diabetes mellitus, particularly with ketoacidosis
- Treatment with glucocorticoids
- Hematologic malignancies
- Hematopoietic cell transplantation
- AIDS
- Injection drug use
- Trauma/burns
- Malnutrition

The most common occurrence is nasal mucus, which occurs when the fungus enters the sinuses through inhalation. The most common symptom we encounter in the clinic is nosebleeds. Headache, nasal sores and nasal congestion may be other clinical symptoms. The second most common form of mucormycosis is lung infection after inhaling the fungus. Pulmonary infection occurs most frequently in patients with neutropenia.

Hemophagocytic syndrome is a hyperinflammatory state caused by overstimulated but dysregulated and often ineffective immune responses.In HLH, NK cells fail to eliminate activated macrophages. This results in excessive CD8+ T cell and macrophage activation and elevated levels of interferon gamma and other cytokines leading to HLH pathology. In addition to antigen presentation and cytokine production, macrophages can also phagocytose host cells. Hemophagocytosis is part of the sepsis syndrome caused by severe infection. Hemophagocytosis may be seen in tissue biopsies (lymph nodes, spleen, liver) or bone marrow aspirates/biopsies.

clinical findings:

- Fever
- Splenomegaly
- Bicytopenia
- Hypertriglyceridemia or hypofibrinogenemia
- Ferritin >500 mcg/

Case Report

A 59-year-old male patient applied to our hematology department due to pancytopenia in the blood results obtained from an external center. The patient was diagnosed with AML as a result of the examinations and bone marrow aspiration.

The patient followed as AML 7+3 treatment protocol has been planned. The patient received antibiotic treatment for various reasons while receiving chemotherapy. After receiving treatment, the patient was deemed suitable for bone marrow transplantation. Approximately 1 month after the bone marrow transplantation, the patient started to complain of skin rash, fever, diarrhea and vomiting. As a result of the biopsy taken from the patient's skin by dermatology, Graft versus host disease grade 2 was determined. The patient was routinely followed up by the infectious diseases department and the stool tests were positive for CMV PCR and treatment was started. Hepatomegaly was detected in the patient's abdominal USG results. The patient had neutropenia and received antibiotic treatment due to infection during this period. The patient complained of nosebleeds and the ear, nose and throat department was consulted. During the examination, a lesion was observed in the nasal septum and a biopsy was taken. The biopsy result was urgently evaluated by pathology and the result was

mucormycosis.The patient was taken into surgery. He continued to be intubed in the ICU. mucor treatment was started The patient was intubated and monitored in intensive care for a while. A peripheral blood smear was taken from the patient and phagocytosed macrophages were observed in the smear. The patient's peripheral blood smear and laboratory results were compatible with hemophagocytosis syndrome disease. Extubation of the patient was planned, but the patient did not wake up. The patient was followed in the intensive care unit and exitus within a few days.

LAB:

Hdl cholesterol:6 mg/dl
Cholesterol:5 mg/dl
Ldl cholesterol:164 mg/dl
Vldl cholesterol:76 mg/dl
Triglyceride:381 mg/dl
Fibrinojen:439,69 mg/dl
Ferritin:27781 pg/ml
Creatinine 1,5 mg/dl
Sodium (na) 141 mmol/l
Potassium (k) 3,76 mmol/l
Chlorine (cl) 99 mmol/l
Calcium (ca) 6 mg/dl
Phosphorus (p) 6,5 mg/dl
Wbc 0.47 10^3/ul
Hgb 9.00 g/dl
Ly# 0.020 10^3/ul
Mcv 82.50 fl
Mo# 0.02 10^3/ul
Ne# 0.43 10^3/ul
Plt 95.00 10^3/ul

Discussion and conclusions

Acute Myeloid Leukemia (AML) is malignancy of the white blood cells that leads to bone marrow failure and organ infiltration. Untreated, AML is fatal and life-threatening.[3]

Mucormycosis, caused by opportunistic pathogenic fungi, is a difficult-to-diagnose with high mortality that commonly occurs in patients with impaired immune status, particularly those with diabetes mellitus, hematological malignancy, and neutropenia.[4]

If patients with pencetopenia and low immune system have fever of unknown reason, hemophagocytosis syndrome may be considered.[8] In HLH, NK cells fail to eliminate activated macrophages. This results in excessive CD8+ T cell and macrophage activation and elevated levels of interferon gamma and other cytokines leading to HLH pathology.

After our patient was diagnosed with AML, chemotherapy treatment started. The patient had entered pancytopenia due to chemotherapy. Patient who developed GVHD after transplantation ,the extended duration of hospitalization caused a patient with a low immune system to be mucor. our patient had both mucor and hemophagocytosis syndrome and both are mortal. Unfortunately he passed away.

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Research Article

Open radical prostatectomy and laparoscopic radical prostatectomy: perioperative comparison of the procedures

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Abstract: Radical prostatectomy is seen as one of the main methods for the treatment of prostate cancer and has been performed for more than 150 years, being considered the gold standard for the treatment of localized disease. In recent years, laparoscopic and robot-assisted access has received notoriety, with oncological results similar to the open technique associated with the benefits of the minimally invasive approach. Aim: To compare complications and perioperative complications in patients undergoing radical open prostatectomy with the laparoscopic approach. Method: This is a retrospective data analysis performed by reviewing the electronic medical records of patients diagnosed with localized prostate cancer at the Regional Hospital of Vale do Paraíba, SP, Brazil (HRVP). Data were collected regarding the procedures performed from January 2014 to December 2018, totaling 35 patients undergoing Laparoscopic Radical Prostatectomy and 35 patients undergoing Open Radical Prostatectomy. Intra and perioperative data were analyzed, specifically the surgical time, blood transfusion rate, type and time of drainage of the surgical site, and length of hospital stay. The data were subsequently analyzed, and the results of both techniques were compared. Results: When comparing the averages of operative times, we obtained a variation rate of 26.2%. The calculated p-value was 0.00002, demonstrating that the operative time in the open group was significantly shorter. When comparing the mean time taken to remove the drain, we observed a variation rate of 37.8%. The calculated p-value was 0.00004, this time being statistically shorter in the laparoscopy group. The other variables evaluated did not show statistical significance between the groups. Conclusion: The main advantage of an open group is that the procedure can be performed in less time. The main advantage of the laparoscopic group was the possibility of removing the drain before patients were operated on by PRA.

Keywords: surgery; prostatectomy; open surgery, robotic prostatectomy, prostatitis

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1. Introduction

In Brazil, prostate cancer is the second most common cancer among men, less frequent only than non-melanoma skin cancer (1). It is considered a cancer of the elderly, with 75% of cases occurring in patients over the age of 65. An increase in the incidence rate of prostate cancer has been observed in Brazil, possibly due to greater access to imaging tests, greater access of the population to the health system, and increased life expectancy. There are an estimated 65,840 new cases, with 15,576 deaths in 2020 alone (2).

Radical prostatectomy is seen as one of the main methods for treating prostate cancer and has been performed for more than 150 years, being considered the gold standard for the treatment of localized disease (1). In the late 1970s and early 1980s, anatomical studies provided important information on periprostatic anatomy, contributing to better oncological, perioperative, and postoperative outcomes. The technique was standardized by Eggleston and Walsh (3), which presented excellent perioperative, oncological, and postoperative functional results (1,4,5).

Despite greater anatomical knowledge, retropubic radical prostatectomy is still associated with significant morbidity, including bleeding, postoperative pain, thromboembolism, urinary incontinence, erectile dysfunction, and ureterovesical anastomotic stenosis (6).

In recent years, laparoscopic and robotic-assisted access has received notoriety, with oncological results similar to the open technique associated with the benefits of the minimally invasive approach. Laparoscopic access was introduced in order to reduce perioperative morbidity, but it is known that the learning curve is high (1). To illustrate the above, Secin et al.(7) analyzed 8544 consecutive surgeries performed by 51 surgeons and demonstrated that the rate of positive margins reached a plateau with only 250 procedures. Carvas et al.(8) demonstrated that surgeons with high surgical volume had lower rates of blood transfusion, postoperative incontinence, erectile dysfunction, length of hospital stay, and urethrovesical anastomotic stenosis (4). In another study, it was evidenced that the rate of cancer recurrence was substantially reduced with increasing surgeon experience with laparoscopy. The same study also reported that experience in open prostatectomies did not reduce the learning curve in laparoscopic prostatecuses (9). However, it should be noted that what weighs against the laparoscopic approach is the long learning curve, minimized by robotic surgery(1,4,10). Robotic surgery has been growing in recent years, especially in developed countries and large medical centers. Prostatectomy is one of the most commonly performed surgeries with robotic access. In the United States, more than 70% of prostatectomies are performed in this way. However, there is no clear evidence of better oncological and functional results of this technique. The main advantages of robotic access are related to the improvement of ergonomics during surgery. As a negative point of robotic-assisted surgery, the considerable financial increase that the technique requires is highlighted(6,10–12).

Based on the above, the relevance of the present study is observed, especially nowadays, in which better surgical results in prostate cancer are sought, and the role of laparoscopic access in times when robotic surgery has been gaining notoriety.

2. Materials and Methods

The study is a retrospective analysis of data, carried out through a review of the electronic medical records of patients diagnosed with localized prostate cancer, at the Regional Hospital of Vale do Paraíba (HRVP). The surgical procedures were performed by physicians from the urology team of the HRVP. The project of this study was submitted and authorized by the ethics committee of the Institute of Education and Research of the HRVP.

Data were collected regarding procedures performed from January 1, 2014 to December 31, 2018, totaling 35 patients who underwent Laparoscopic Radical Prostatectomy (LRP) and 35 patients who underwent Open Radical Prostatectomy (ARP). Patients undergoing PRA were selected in pairs with patients undergoing PRL (surgeries performed on close dates), because in the period there was a considerably higher number of RPAs. The surgical procedures were indicated by urologists attending the HRVP after review of clinical data and clearance by the anesthesia team. Patients considered clinically unfit in the surgical risk assessment were referred for treatment with alternative therapies. The open technique was based on the classic description standardized by Walsh (13). The laparoscopic technique was performed with extraperitoneal access. In all PRAs, the drain used in the postoperative period was the vacuum suction drain (Portovac). The Penrose drain was used in all PRLs.

Intraoperative and perioperative data were analyzed, specifically surgical time, blood transfusion rate, type and time of surgical site drainage, and length of hospital stay. The data were later analyzed, comparing the results of both techniques. Numerical variables were presented by a measure of central tendency (mean or median), followed by their respective measure of dispersion (minimum and maximum values, and standard deviation). Categorical variables were presented as absolute and relative frequency.

3. Results

Group 1 – Patients undergoing PRA

In the analysis of the data of the 35 patients submitted to PRA, we found a range in age from 49 to 71 years, with a median of 63 years and a mean of 62.3 ± 6.2 years.

Prostate volume ranged from 19 to 70 cm³, with a median of 40 and a mean of 39.1 ± 13.1 cm³.

Regarding the operative time, a variation from 135 to 275 minutes was observed, with median of 190 minutes and mean of 195 ± 29.4 minutes.

A blood transfusion rate of 3% (n = 1) was observed. A variation of 3 to 7 days in the length of hospital stay was observed, with a median of 4 days and a mean of 4 ± 1 day. The drain removal time ranged from 3 to 11 days, with a median of 4 and a mean of 4.5 ± 2 days (Table 1).

Table 1: Group 1 - Patients undergoing PRA

	Time of surgery (minutes)	Age (years)	Prostate volume (cm³)	Days of Hospitalisation	Probe Removal Time (days)
Minimum	135	49	19	3	3
Maximum	275	71	70	7	11
Median	190	63	40	4	4
Average ± DP	195 ± 29,4	62,3 ± 6,2	39,1 ± 13,1	4 ± 1	4,5 ± 2

Source: data collected by the author.

Group 2 - Patients undergoing PRVL

In the analysis of the data of the 35 patients submitted to PRL, an age range from 48 to 76 years was found, with a median of 61 and a mean of 61.4 ± 7.8 years.

Prostate volume ranged from 12 to 81 cm³, with a median of 40 and a mean of 38.5 ± 12.5 cm³.

Regarding the operative time, a variation from 135 to 460 minutes was observed, with a median of 250 and a mean of 264.1 ± 78.5 minutes.

A blood transfusion rate of 3% (n = 1), conversion to PRA of 6% (n = 2), and rectal injury of 3% (n = 1) were identified. A variation of 3 to 8 days was observed at the time of hospitalization, with a median of 4 and a mean of 4 ± 1.1 days. On the other hand, the drain removal time ranged from 2 to 7 days, with a median of 3 and a mean of 2.8 ± 1.1 days (Tables 2).

Table 2: Group 2 - Patients undergoing PRVL

	Time of surgery (minutes)	Age (years)	Prostate volume (cm^3)	Days of Hospitalisation	Probe Removal Time (days)
Minimum	135	48	12	3	2
Maximum	460	76	81	8	7
Median	250	61	40	4	3
Average ± DP	264,1 ± 78,5	61,4 ± 7,8	38,5 ± 12,5	4 ± 1,1	2,8 ± 1,1

Source: data collected by the author.

Comparison between PRA and PRL patients

The test used to compare the variables was the *unpaired t-test, considering the parametric distribution of the data (verified by the* Kolmogorov Smirnov test performed in Microsoft Excel®). A significance level of 95% was defined, and comparisons with *a p-value* lower than 0.05 were considered statistically different.

In the comparison of the mean ages, there was a variation of 1.4%. The *calculated p-value* was 0.625. Since the p-value was > 0.05, the difference between the means was not significant.

Comparing the mean volumes of the prostates, a variance rate of 1.5% was obtained. The *calculated p-value* was 0.828, also without statistical significance.

When comparing the mean operative times, a variation rate of 26.2% was obtained. The *calculated p-value* was 0.00002, demonstrating that the operative time in PRA was significantly shorter.

In the comparison of blood transfusion rates, a rate of 3% (n=1) was identified in both methods, with no statistically significant difference ($p = 1$).

When comparing the mean length of hospital stay, no rate of variation was found, as both procedures had an approximate mean length of stay of 4 days. The p-value calculated for the mean length of hospital stay was 0.482, with no statistical significance.

Finally, in the comparison of the meantime for drain removal, the variation rate was 37.8%. The *calculated p-value* was 0.00004, which was statistically shorter in the PRL group.

The comparisons between the groups can be seen in Table 3, which shows the rates of variation between the means of each of the parameters evaluated, in addition to the p-values observed after the application of the *unpaired* Student's t-test.

Table 3: Rates of Variation between Means and P-values of Parameters Evaluated

	Rate of Change between Averages (PRA x PRVL)	p-value
Age	1,4%	0,625 (ns)
Prostate volume	1,5%	0,828 (ns)
Surgery time	26,2%	0,00002
Length of Hospital Stay	0%	0,482 (ns)
Drain Removal Time	37,8%	0,00004
Haemotransfusion	0 %	1 (ns)

ns = not significant.

Source: data collected by the author.

4. Discussion

Radical Prostatectomy (RP) is considered the gold standard method for the treatment of localized prostate cancer (14). The PR was introduced by Young (15), and revised by Millin

(16). However, Walsh et al.(13) described new technical aspects of the surgery, establishing standardization for the procedure in question.

The learning curve is essential to minimize perioperative and postoperative complications, as well as to reduce surgical time(14,17). Salomon et al. (18) reported a mean surgical time of 197 minutes through the suprapubic approach. Saito et al.(14) showed a mean surgical time of 140 minutes, considering surgeries performed by residents in training. In our study, an average of 195 minutes of surgical time was observed, which is consistent with what has been found in the literature.

Regarding the rate of blood transfusion in Open Radical Prostatectomy, we showed a blood transfusion rate of 3%. In other studies, Coelho (4) reported a rate of 5.7%, with an estimated mean bleeding of 600 ml. Saito et al.(14), on the other hand, showed a blood transfusion rate of 7.2%, with a mean bleeding of 488 ml. Amorin et al.(17), in their study, observed a blood transfusion rate of 11.1%.

Laparoscopic Radical Prostatcomia was first described by Schuessler et al.(19), who concluded that the procedure was not a good alternative due to the long surgical time and inferior results to the open technique. From then on, there was a great improvement in perioperative morbidity related to the laparoscopic technique (20).

In our analysis, the mean time found in PRL (all by extra pectoral access) was 264 minutes. In his presentation, Siqueira Júnior (20) demonstrated a mean surgical time of 175 minutes in transperitoneal laparoscopic radical prostatectomy and 267.6 minutes in extraperitoneal access. He also reported a conversion rate and rectal injury rate of 2.5% in both techniques. Regarding the rate of blood transfusion, it was found to be 5% in the transperitoneal access and 12.5% in the extraperitoneal access. The mean length of hospital stay reported by the author was 3 days in both techniques.

Mariano et al.(21) published a series of 730 patients submitted to PRL, in which they showed a mean surgical time of 124.97 minutes, a mean length of hospital stay of 4.3 days, and a blood transfusion rate of 5.4%. Comparing our data, we observed a lower blood transfusion rate than what is reported in the literature, both in the Mariano et al (21) and Siqueira Junior (20) reports. Rassweiler et al.(6) published a comparison between 219 patients who underwent open radical prostatectomy and 521 patients who underwent laparoscopic radical prostatectomy. The authors showed a significantly shorter surgical time in the open technique, although the rate of blood transfusion was lower in the laparoscopic approach. Results are similar to those of our study, in which we observed a shorter surgical time in the PRA group, with statistical significance.

Venkatesh et al.(22) demonstrated a series of 361 patients who underwent extraperitoneal surgery performed by an experienced surgeon, with a mean surgical time of 190 minutes and a mean hospital stay of 1.28 days. Bollens et al.(23) showed a mean surgical time of 317 minutes in extraperitoneal surgeries, with a blood transfusion rate of 13%.

Vickers et al.(9), in a multicenter and retrospective study, reported that surgeons with more than 100 laparoscopic prostatectomies performed had better postoperative oncological results, showing that this technique presents a large learning curve to achieve satisfactory perioperative and oncological results.

Bollens et al.(23) compared open radical prostatectomy with laparoscopic and robotic prostatectomy. The authors' blood transfusion rate was 21% in open cases, 4.6% in laparoscopic cases, and 1.8% in robotic cases.

In our exposure, there was no great variation in prostatic volume, which hindered a specific analysis of this item. Chang et al.(24) showed in their publication that the volume of the prostate did not modify the length of hospital stay or the rate of blood transfusion. The mean surgical time was 14 minutes longer, but not statistically significant.

Rassweiler et al.(25) reported that the main benefits of robotic access over laparoscopic access are the surgeon's ergonomics and the lower learning curve. In addition, the learning curve of laparoscopic access has been shown to be long, in which the surgeon needs around 250 procedures to present better perioperative and oncological results (26). This fact is important in our study because the surgeons responsible for the laparoscopic procedures experienced a learning curve during the period, which may have contributed to a discrepancy in the results compared to the open one, especially during surgical time.

With greater access to the use of robots to perform prostatectomies, especially in large centers, there is a clear trend towards a decrease in laparoscopic prostatectomies, although this is still a more affordable method with perioperative and oncological results similar to robotics. It is worth noting, however, that the open approach is still important in the therapeutic arsenal of prostate cancer, especially in less developed and economically unfavorable centers.

5. Conclusions

In our study, we observed that the main advantage of PRA is that the procedure is performed in a shorter time. Regarding PRL, the main statistical evidence was the earlier removal of the drain in the postoperative period. Despite the small number of patients included in this study, the results call attention to the advantages of each of the methods evaluated, and as discussed, we present results similar to those found in the literature. It is suggested that further studies be conducted, with a larger sample and better control of preoperative, intraoperative and postoperative parameters, in order to verify whether the results observed here can be repeated when evaluated on a larger scale.

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