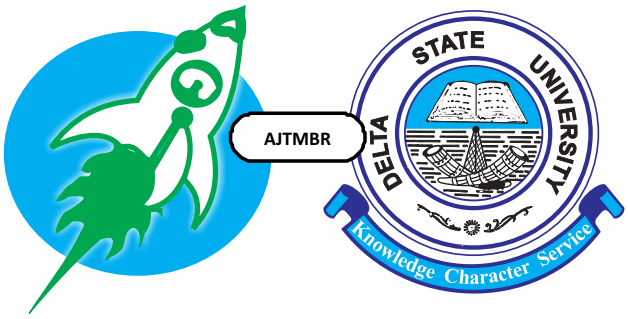
African Journal of Tropical Medicine and Biomedical Research (AJTMBR)



The Journal is the Official Publication of the College of Health Sciences, Delta State University, Abraka, Nigeria.

ISSN: 2141-6397

Focus and Scope

The African Journal of Tropical Medicine and Biomedical Research is a multidisciplinary and international journal published by the College of Health Sciences, Delta State University of Abraka, Nigeria. It provides a forum for Authors working in Africa to share their research findings on all aspects of Tropical Medicine and Biomedical Sciences and to disseminate innovative, relevant and useful information on tropical medicine and biomedical sciences throughout the continent. The journal will publish original research articles, reviews, editorials, commentaries, short reports, case reports and letters to the editor. Articles are welcome in all branches of medicine and dentistry including basic sciences (Anatomy, Biochemistry, Physiology, Pharmacology, Psychology, Nursing etc) and clinical sciences (Internal Medicine, Surgery, Obstetrics and Gynaecology, Dental surgery, Child Health, Laboratory Sciences, Radiology, Community Medicine, etc). Articles are also welcome from social science researchers that document the intermediating and background social factors influencing health in countries of Africa. Priority will be given to publication of articles that describe the application of the principles of primary health care in the prevention and treatment of diseases.

Editorial Notices

The journal will be published biannually in the months of March and September. Annual subscription fee in Nigeria is two thousand naira (N2,000) per volume (2issues); One-thousand-naira single copy (N1000). The annual subscription rate for other parts of the world is as follows: United Kingdom £60 (post free). West Africa $60 (post free). The rest of the World and the United States of America $120 (post free). A charge of $60 is made for reprints inclusive of postage. Cheques should made payable to the African Journal of Tropical Medicine and Biomedical Research and addressed to the Editor-in-Chief.

Journal Contact

All correspondence, including manuscripts for publication (in triplicate) should be addressed to:

Professor P.S. Igbigbi
The Editor-in-Chief,
Department of Anatomy,
Faculty of Basic Medical Sciences,
College of Health Sciences,
Delta State University, Abraka,
Delta State, Nigeria.

Or:
Professor Lawrence Omo-Aghoja
Editor
Department of Obstetrics and Gynecology,
Faculty of Clinical Medicine,
Delta State University, Abraka, Nigeria.
Email: journalajtmbr@yahoo.com
Cc: all email to
eguono_2000@yahoo.com
Tel: 08039377043

All authors are advised to submit an electronic copy in CD-ROM along with a hard copy of their manuscript, as this will spare remarkable time in the reviewing and typesetting processes.

In the alternative, authors can submit their articles and covering letter by email attachments. A covering letter (signed by all authors) accompanying the manuscript should certify that the article has not been previously published and is not being considered for publication elsewhere.

Information for Authors

All manuscript are peer-reviewed and accepted with the understanding that the work has not been published or being considered for publication elsewhere. Indeed, the authors would be requested

to sign a copyright form transferring the ownership of the paper to the African Journal of Tropical Medicine and Biomedical Research. All articles must include the correct names and addresses of author(s) including e-mail addresses and telephone numbers. Articles will be subjected to a thorough peer review process before any decision is made to publish or not. Authors should note that the African Journal of Tropical Medicine and Biomedical Research is not under any obligation to publish articles submitted, as decision to publish will be based on recommendations of reviewers and the editorial advisory board.

Manuscripts

Articles submitted for publication should be typed double-spaced with 2.5cm margins with accompanying CD-ROM in Microsoft Word format for easy and quick peer review and typesetting. Each of the following sections should begin in a new page: title page, abstract, introduction, materials and methods, results, discussion, acknowledgment (s), references, tables, legends to figures and illustrations. The manuscript should include:

Title Page

The title page should include the following information: 1. the title and sub-title; 2. the name(s) of the author(s); 3. the affiliation(s) of the author(s); 4. name and address of the corresponding author and 5. three to six key words for indexing and retrieval purposes.

Abstract

The abstract should be structured and not more than 250 words. It should carry the following headings: Introduction, Materials and Methods, Results and Conclusion.

Original Research- The journal welcomes articles reporting on original research, including both quantitative and qualitative studies. Full-length articles should generally not exceed 3000 words, excluding abstract, tables, figures, and references. The subject matter should be organised under appropriate headings and sub-headings as itemized above.

Review Articles- Comprehensive review articles on all aspects of tropical medicine and biomedical sciences will also be considered for publication in the journal. Reviews should provide a thorough overview of the topic and should incorporate the most current research. The length of review articles must not exceed 3,000 words and the organisational headings and sub-headings used are at the author's discretion.

Short Reports - Brief descriptions of preliminary research findings or interesting case studies will be considered for publication as short reports. The length of the abstract and article should be restricted to 150 and 2,000 words respectively and organisation of short reports are left to the author's discretion.

Commentaries or Editorials- Commentaries or editorials on any aspect of tropical medicine and biomedical sciences in Africa will be considered for publication in the journal. Opinion pieces need not reference previous research, but rather reflect the opinions of the author(s). The length should not exceed 2,000 words.

Tables and Figures

All tables and figures should be submitted on separate sheets of paper and should be clearly labelled. Coloured tables and figures may be reprinted in black and white. Authors should especially take care that all tables are clear and understandable by themselves, independent of

the text. A reader should be able to read only the tables and easily grasp all information without the text.

Acknowledgments

Acknowledgments should be included on a separate sheet of paper and should not exceed 100words. Funding sources should be noted here.

References

References should be in the Vancouver style and numbered consecutively in the order in which they are mentioned in the text. Titles of journals should be abbreviated according to the Index Medicus style. Authors must cross-check and make sure that all information provided in the reference list is complete and correctly written. Reference numbers should be inserted above the line on each occasion a reference is cited in the text, e.g., … as 1-3 reported in other studies. Numbered references should appear at the end of the article and should include the names and initials of all authors. The format of references should be as published by the International Committee of Medical Journal Editors in the British Medical Journal 1988, volume 296, pages 401-405. The following are sample references for an article published in a journal and for a book: Ahmed Y, Mwaba P, Chintu C, Grange JM, Ustianowski A, Zumla A. A study of maternal mortality at the University Teaching Hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause of maternal death. Int J Tuberc Lung Dis 1999; 3: 675-680. Whitby LG, Smith AF, Beckett GJ. Enzyme Tests in Diagnosis. In: Lecture Notes on Clinical Chemistry. Whitby LG, Smith AF & Beckett GJth (eds). 4 editions. Blackwell Scientific Publications. 1988. 103-127.

Units of Measurement

All measurements should be expressed in SI (Systeme International) Units.

Galley proofs

Corrections of galley proofs should be strictly restricted to Printer's error only. Orders for offprints should be made when the corrected proofs are being returned by the authors. Articles accepted for publication remain the property of the journal and can only be reproduced elsewhere in line with section 5 of the copyright agreement.

Table of Contents

Hyperglycemic emergencies in a tertiary health facility: clinical presentation and predictors of mortality

Beatrice Ohunene Bello-Ovosi[1], Joseph Ogirima Ovosi[2], Isa Kweumpo Bansi[3],

Abstract

Aim: To assess the clinical presentations and predictors of mortality of hyperglycemic emergencies (HE) in persons with diabetes mellitus (DM) presenting in a tertiary health facility in Nigeria.

Methods: This was a two-year retrospective review of hospital records of persons with DM in a tertiary hospital in Nigeria. We retrieved data on person's demographics, clinical and laboratory characteristics into Microsoft Excel and analyzed with STATA version 14.

Results: A total of 195 (42.4%) out of 460 persons admitted with DM fulfilled the eligibility criteria. Diabetic ketoacidosis (DKA) was present in 42.6%, mixed hyperglycemic emergency (MHE) in 34.9% and hyperglycemic hyperosmolar state (HHS) in 22.5%. Mortality in HE was 8.7%. The common clinical presentation were: osmotic symptoms (71.3%), tachypnoea (46.7%), tachycardia (42.6%). Elevated anion gap (89.2%) and anemia (80.5%) were the common laboratory findings. Infections (86.7%), non-compliance (79.5%) and newly diagnosed DM were the common precipitants of HE. Significant predictors of mortality were: duration of DM between 5-9 years, Glasgow Coma Scale (GCS) < 8, hypotension, and hypokalemia.

Conclusion: HE is still a common cause of hospitalization and mortality in persons with DM; and features such osmotic symptoms, tachypnea and high anion gap metabolic acidosis should alert the clinician.

Keywords: Hyperglycemic emergencies, diabetes ketoacidosis, hyperglycemic hyperosmolar state, mortality

[1] *Department of Internal Medicine, Kaduna State University/Barau Dikko Teaching Hospital, Kaduna, Nigeria*
[2] *Air Force Institute of Technology, Kaduna, Nigeria, 461 Nigerian Air Force Hospital, Kaduna, Nigeria*
[3] *National Industrial Court Clinic, Abuja, Nigeria*

Corresponding author: Joseph Ogirima Ovosi, Air Force Institute of Technology, Kaduna

1. Introduction

In 2019, the global estimate of persons with diabetes mellitus (DM) was 463 million, out of which 19 million were living in Africa; and DM was responsible for 366,200 deaths (6.8% of all-cause mortality) in the sub-region.[1] Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are two of the extreme life-threatening and overlapping spectrum of acute metabolic complications, termed hyperglycemic emergencies (HE), which are largely seen in people with uncontrolled DM; and contribute significantly to the morbidity and mortality attributed to the disease.[2,3]

In DKA, absolute or relative insulin deficiency is accompanied by increase in counter-regulatory hormones resulting in hyperglycemia, ketonemia and acidosis.[4] HHS, however, results from relative insulin deficiency and/or insulin resistance which

leads to marked hyperglycemia, severe extracellular volume contraction, hyperosmolality usually > 320 mOsmol/kg and minimal ketonemia.[2,5,6] While in DKA, the insulin deficiency is marked enough to stimulate lipolysis and ketogenesis which are its hallmark; in HHS, the insulin deficiency is not marked enough, hence, the minimal ketonemia seen.[7]

The majority of the people with DM are undiagnosed and could present for the first time with HE,[8-11] and this may be worse in Africa, where about 59.4% of people living with DM are undiagnosed.[1] In the UK, about one-quarter of the diagnosis of type 1 DM are made for the first time in the presence of DKA, resulting in an expenditure of 1,387GBP per hospitalization; and up to 20% of HHS do not have previous diagnosis of DM.[1,12] In the US, hyperglycemic emergencies accounted for 207,000 hospitalizations in 2014, and 168,000 of these were due to DKA, accounting for 7,470-20,864 USD per hospitalization.[13,14] In Nigeria, the exact burden of HE is not known. However, hospital-based studies have reported incidences in the range 11 – 40%,[15-17] and mortality in the range 18-22% for DKA and 25-35% for HHS.[18,19] Despite the high morbidity and mortality attributed to HE in Nigeria, few studies have assessed the clinical presentations and the factors that predict mortality among them. This study, therefore, assessed the clinical presentations and predictors of mortality in persons with HE in Ahmadu Bello University Teaching Hospital (ABUTH), Zaria – a tertiary health facility in Nigeria.

2. Methods

2.1 Study Area

ABUTH is a 500-bed public tertiary health facility located in Zaria, northwestern Nigeria. It serves clients from most northern Nigerian states and neighboring countries of Niger and Chad Republics.

2.2 Study design

We conducted a retrospective review of hospital records of all adult patients admitted for HE at ABUTH, Zaria over two years, from 1 January 2015 – 31 December 2016.

2.3 Study population

Subjects were considered eligible if they were adults aged 18 years and above, and were confirmed to be persons with DM by the admitting physician and presenting with hyperglycemic emergency during the period. Pregnant women and patients with incomplete information were excluded from the study.

2.4 Data collection

Data was extracted using a structured-questionnaire that included sections on socio-demographics, clinical and laboratory information. Clinical and laboratory data retrieved were: type of DM, duration of DM, number and types of anti-diabetic medications, compliance, past history of HEs, co-morbidities, presenting symptoms, physical examination findings, serum urea and electrolyte and complete blood count. The primary outcome measure was in-hospital mortality due to HE.

2.5 Measurement of variables

DKA was defined as blood glucose between 16.6 – 33.3 mmol/L, serum bicarbonate (HCO_3^-) ≤ 18 mmol/L and urine dipsticks ketones of at least +2.[20] HHS was blood glucose > 33.3 mmol/L, serum HCO_3^- > 18 mmol/L, serum osmolality > 320 mmOsm/kg and absence of urine dipsticks ketones or urine dipsticks ketones of not more than +1.[2,3] Mixed hyperglycemic emergency (MHE) was admitting blood glucose > 16.6 mmol/L, serum HCO_3^- < 18 mmol/L, serum osmolality < 320 mmOsmol/kg and absent or

urine dipsticks of +1.[4, 21] Type 1 DM referred to patients with DM who had been on insulin since diagnosis and required insulin for survival and type 2 DM were patients with DM who were previously managed on lifestyle modification, or on oral hypoglycemic agents; or insulin-requiring patients who initially were not insulin-dependent.[19] Osmotic symptom was documented history of polyuria, polydipsia and/or weight loss. Fever was admitting oral temperature > 37.2^{0}C and hypothermia, oral temperature < 36.4^{0}C.[22,23] Tachycardia was admitting pulse rate > 100 beats/minute,[24,25] and tachypnea admitting respiratory rate > 20 cycles/minute.[26] Alteration in sensorium was mild, if Glasgow Coma Scale (GCS) was 13-15; moderate if 9-12 and severe if £ 8.[27] Hypertension was defined as systolic blood pressure of ≥140 mmHg or diastolic blood pressure ≥90 mmHg or a documentation of treatment with anti-hypertensive medications[28]; hypotension was blood pressure recording of ≤ 90/60 mmHg.[29]

Electrolyte parameters were defined as follows: Hypernatremia, serum sodium (Na^+) > 142 mmol/L; hyponatremia, serum sodium < 135 mmol/L.[30] Hyperkalemia, serum potassium (K^+) > 5.0 mmol/L; and hypokalemia, serum potassium < 3.5 mmol/L.[31] Acidosis was serum HCO_3^- ≤ 18 mmol/L and further classified as mild when bicarbonate was 15 – 18 mmol/L, moderate when 10 – 14 mmol/L and severe when < 10 mmol/L.[20] Serum anion gap was calculated from the formula: $(Na^+ + K^+) – (Cl + HCO_3)$ and classified as high, if > 18 mEq/L.[32] Serum osmolality was calculated from the formula: 2 (Na^+) + glucose (mmol/L) + Urea (mmol/L), and classified as high if > 320 mmOsm/kg.[33] Leucocytosis was white blood cell count (WBC) > 12.0 × 10^9 /L and leucopenia as counts < 4.0 × 10^9 /L.[34] Anemia was defined as hemoglobin (Hb) < 12g/dL and elevated urea, serum urea > 8.6 mmol/L.[35] Compliance – referred to admittance to taking anti-diabetic medications for more than 75% of the drug schedule time as at the time of admission or adhering to the dietary regimen prescribed for most of the days of the month in the preceding three months.

2.6 Statistical analysis

Data were coded and entered into STATA version 14 (Stata Corp, College Station, Texas) for analysis. Continuous variables were expressed as means ± standard; and categorical variables, as frequencies and percents. Student's t test and one-way analysis of variance (ANOVA) were used to test association with continuous outcome variables; and Chi square test and Fisher's exact test were for categorical outcome variables. Multivariate logistic regression was used to identify independent predictors of mortality by entering variables with $p < 0.25$ on bivariate analysis into the model, and variables with $p < 0.05$ were considered statistically significant.

2.7 Ethical Approval

We sought and obtained ethics approval for the conduct of the research and the use of data from ABUTH Research Ethics Committee (ABUTH-REC), and permission for use of the data from the medical records. We did not obtain a written informed consent from the subjects due to the retrospective nature of the study, but we maintained privacy and confidentiality by ensuring that each case file was assigned a unique numerical identifier for tracking purposes only; and data was retrieved anonymously.

3. Results

3.1 Summary of study enrolment

A total of the 460 persons with DM were admitted during the study period, out of which

195 (42.4%) fulfilled the eligibility criteria and had complete data for analysis. Eighty-three (42.6%) of this had DKA, 68 (34.9%) had MHE and 44 (22.5%) had HHS. The overall mortality of HE was 17 (8.7%); 7 (8.4%) in DKA; 6 (13.6%) in HHS and 4 (5.9%) in MHE (Figure 1).

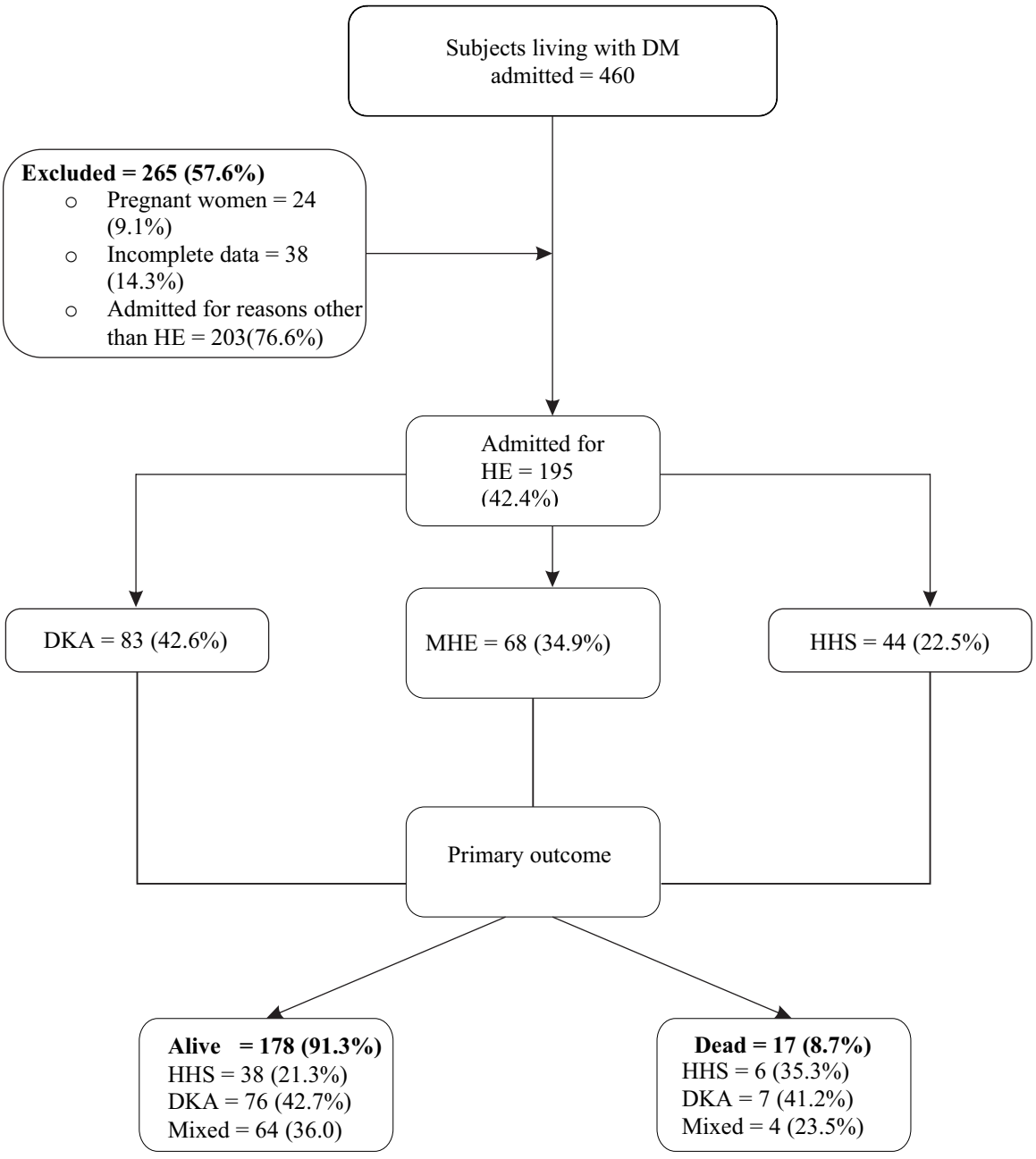


Figure 1: Summary of flow chat of participants

3.2 Background characteristics of patients with hyperglycemic emergencies

The mean age of the subjects was 53.6 ± 14.5 years. Majority (56.9%) of subjects were aged 41 – 64 years while only 46 (23.6%) were aged ³ 65 years. One hundred and forty-six (74.9%) were males and 145 (74.4%) belong to the Hausa/Fulani ethnic group. A significant proportion (94.4%) had type 2 DM, and 108 (55.4%) were on some treatment for DM with only 41 (21.0%) having good compliance. Eighty (41.0%) had previous episodes of HE and 107 (54.9%) patients had at least one co-morbidity (Table 1).

3.3 Clinical and laboratory characteristics of hyperglycemic emergencies

One hundred and thirty-nine (71.3%) of persons with HE had osmotic symptom; 47 (24.1%) had lassitude, 23 (11.8%) had dysuria, 17 (8.7%) had nausea/vomiting, 15 (7.7%) had muscle aches and 7 (3.6%) had headache.

Tachypnoea was the commonest sign and was present in 91 (46.7%) of persons with HE and this was followed by tachycardia, 83 (42.6%); fever, 82 (42.0%); foot ulcer/sepsis, 78 (40.0%); and hypertension, 61 (31.3%). All persons with HE had some degree of alteration in sensorium, but overall, 22 (11.3%) had moderate-severe impairment (14.4% in DKA vs. 18.2% in HHS vs. 2.9% in MHE, p = 0.012). Twenty (10.3%) had hypothermia and 14 (7.2%) had hypotension (Tables 2 and 3).

High anion gap was the commonest laboratory finding, occurring in 174 (89.2%) of persons with HE (98.8% in DKA vs. 81.8% in HHS and 82.3% in MHE, p = 0.001). Others were: anaemia, 157 (80.5%); hyponatremia, 67 (34.4%); elevated urea, 62 (31.8%); leukocytosis, 57 (29.2%); acidosis, 54 (27.7%); hyperkalemia, 32 (16.4%); hyperosmolarity, 31 (15.9%); leucopenia, 27 (13.9%); hypernatremia, 20 (10.2%) and hypokalemia, 18 (9.2%).

Table 1: Background characteristics of subjects with hyperglycemic emergencies studied

Characteristics	**Frequency (N =195)**	**Percentage**
Age group, (years)		
≤ 40	38	19.5
41 – 64	111	56.9
≥ 65	46	23.6
Sex		
Female	49	25.1
Male	146	74.9
Ethnicity		
Hausa/Fulani	145	74.4
Others	50	25.6

Employment status		
Unemployed	66	33.9
Employed	129	66.1
Marital status		
Single	47	24.1
Married/Divorced/Separated/Widowed	148	75.9
Type of DM		
Type 1	11	5.6
Type 2	184	94.4
Duration of diagnosis, (years)		
< 5	97	49.7
5 – 9	40	20.5
≥ 10	58	29.7
On treatment for DM		
No	87	44.6
Yes	108	55.4
Compliance with diet/medications		
No	154	79.0
Yes	41	21.0
Past history of HE		
No	115	59.0
Yes	80	41.0
Co-morbidities		
Absent	88	45.1
Present	107	54.9
No of co-morbidities, n = 107		
1	71	66.4
> 1	36	33.6
Type of co-morbidity*		
Hypertensive heart disease	93	47.7
Cerebrovascular accident	19	9.7
Chronic renal failure	21	10.8
Chronic liver disease	7	3.6
Malignancy	5	2.6

DM = Diabetes Mellitus, HE = Hyperglycemic Emergencies, *Note: categories are not mutually exclusive

Table 2: Clinical and biochemical characteristics of subjects with hyperglycemic emergencies studied

Characteristics	**Frequency (N =195)**	**Percentage**
Symptoms		
Osmotic symptoms	139	71.3
Weakness/lassitude	47	24.1
Dysuria	23	11.8
Vomiting	17	8.7
Muscle aches	15	7.7
Headache	7	3.6
Signs		
Tachypnoea	91	46.7
Tachycardia	83	42.6
Fever	82	42.1
Foot sepsis	78	40.0
Hypertension	61	31.3
Moderate-severe altered sensorium	22	11.3
Hypothermia	20	10.3
Hypotension	14	7.2
Laboratory para meters		
Elevated anion gap	174	89.2
Anemia	157	80.5
Hyponatremia	67	34.4
Elevated urea	62	31.8
Leukocytosis	57	29.3

Acidosis	54	27.7
Hyperkalemia	32	16.4
Hyperosmolarity	31	15.9
Leucopenia	27	13.9
Hypernatremia	20	10.3
Hypokalemia	18	9.2

DM = Diabetes Mellitus, HE = Hyperglycemic Emergencies; Note: categories are not mutually exclusive

Table 3: Presentation according to type of hyperglycemic emergencies

Characteristics	**DKA (n = 83)**	**HHS (n = 44)**	**Mixed (n = 68)**	**P value**
Osmotic symptom, n (%)	56 (67.5)	35 (79.5)	48 (70.6)	0.355
Headache, n (%)	1 (1.2)	4 (9.1)	2 (2.9)	0.086
Vomiting, n (%)	9 (10.8)	4 (9.1)	4 (5.9)	0.613
Weakness/lassitude, n (%)	24 (28.9)	11 (25.0)	12 (17.7)	0.270
Muscle aches, n (%)	3 (3.6)	4 (9.1)	8 (11.8)	0.142
Dysuria, n (%)	10 (12.0)	9 (20.5)	4 (5.9)	0.065
Diabetic foot sepsis, n (%)	26 (31.3)	11 (25.0)	33 (48.5)	0.021
GCS, n (%)				0.012
Mild	71 (85.6)	36 (81.8)	66 (97.1)	
Moderate	6 (7.2)	7 (15.9)	2 (2.9)	
Severe	6 (7.2)	1 (2.3)	0 (0)	
Body temperature, n (%)				0.338
Hypothermia	8 (9.6)	3 (6.8)	9 (13.2)	
Normothermia	44 (53.0)	17 (38.6)	32 (47.1)	
Fever	31 (37.4)	24 (54.6)	27 (39.7)	
Anemia, n (%)	65 (78.3)	38 (86.4)	54 (79.4)	0.530

WBC counts, n (%)				0.073
Leucopenia	17 (20.5)	7 (15.9)	3 (4.4)	
Normal	42 (50.6)	25 (56.8)	44 (64.7)	
Leucocytosis	24 (28.9)	12 (27.3)	21 (30.9)	
Tachypnoea, n (%)	47 (56.6)	21 (47.7)	23 (33.8)	0.027
Tachycardia, n (%)	40 (48.2)	22 (50.0)	21 (30.9)	0.053
Blood pressure, n (%)				0.979
Hypotension	7 (8.4)	3 (6.8)	4 (5.9)	
Normotension	49 (59.1)	28 (63.6)	43 (63.2)	
Hypertension	27 (32.5)	13 (29.6)	21 (30.9)	
Elevated Urea, n (%)	34 (41.0)	12 (27.3)	16 (23.5)	0.056
Random blood sugar, mmol/L				0.000
< 16.6	15 (18.0)	1 (2.2)	23 (33.8)	
16.7 – 33.2	36 (43.4)	20 (45.5)	45 (66.2)	
> 32.2	32 (38.6)	23 (52.3)	0 (0)	
Serum Sodium, n (%)				0.001
Hyponatremia	31 (37.4)	6 (13.6)	30 (44.1)	
Normonatremia	48 (57.8)	28 (63.6)	32 (47.1)	
Hypernatremia	4 (4.8)	10 (22.8)	6 (8.8)	
Acidosis, n (%)	39 (47.0)	10 (22.7)	5 (7.4)	0.00
Elevated Anion gap, n (%)	82 (98.8)	36 (81.8)	56 (82.3)	0.001
High Osmolality, n (%)	4 (4.8)	17 (38.6)	10 (14.7)	0.000

(HE = Hypertensive emergencies; DKA = Diabetic Keto Acidosis; MHE = Mixed Hyperglycemic Emergencies)

3.4 Precipitant of hyperglycemic emergencies

The commonest precipitant of HE was infection 169 (86.7%). Others were: non-compliance to dietary advice/medication, 155 (79.5%); newly diagnosed, 47 (24.1%); trauma, 6 (3.1%), and 2 (1.0%) had unknown precipitants. Diabetes foot/hand sepsis 83 (49.1%), urinary tract infection 50 (29.6%), sepsis 12 (7.1%), pneumonia 10 (5.9%), malaria 7 (4.1%), cellulitis 5 (3.0%) and acute diarrhoeal disease 2 (1.2%) were the infections precipitating HE.

3.5 Predictors of mortality in hyperglycemic emergencies

In a univariate analysis, two factors were associated with mortality: Glasgow Coma Scale (p = 0.006) and duration of hospital stay (p = 0.032). The two statistically significant factors, as well as variables with a p-value < 0.25 (Table 4) were selected for the multivariate logistic model. Factors that remained significant were: duration of diabetes between 5 – 9 years (OR = 6.8; 95% CI = 1.1 – 42.1, p = 0.040), GCS < 8 (OR = 10.2, 95% CI = 1.03 – 101.6, p = 0.047), normotension (OR = 0.045, 95% CI = 0.005 – 0.4, p = 0.005), hypertension (OR = 0.067, 95% CI = 0.007 – 0.644, p = 0.019), normokalemia (OR = 0.1, 95% CI = 0.015 – 0.66, p = 0.017), hyperkalemia (OR = 0.04, 95% CI = 0.002 – 0.83, p = 0.038).

Table 4: Outcome of hyperglycemic emergencies by subjects' characteristics

	Outcome		
Characteristics	**Alive (n = 178)**	**Dead (n = 17)**	**P – value**
Age group, n (%)			0.119
≤ 40	37 (20.8)	1 (5.9)	
41 – 64	102 (57.3)	9 (52.9)	
≥ 65	39 (21.9)	7 (41.2)	
Sex (male), n (%)	132 (74.2)	14 (82.3)	0.457
Tribe, n (%)			0.340
Hausa/Fulani	134 (75.3)	11 (64.7)	
Others	44 (24.7)	6 (35.3)	
Employment status, n (%)			0.059
Unemployed	64 (36.0)	2 (11.8)	
Employed	114 (64.0)	15 (88.2)	
Marital status			0.259
Single	41 (23.0)	6 (35.3)	
Married/Divorced/Separated/Widowed	137 (77.0)	11 (64.7)	
Type of DM			0.603
Type 1	11 (6.2)	0 (0)	
Type 2	167 (93.8)	17 (100)	
Duration of Diabetes, years, n (%)			0.173
< 5	92 (51.7)	5 (29.4)	
5 – 9	36 (20.2)	4 (23.5)	
≥ 10	50 (28.1)	8 (47.1)	
Treatment for DM, n (%)	98 (55.1)	10 (58.8)	0.765
Compliance to treatment, n (%)	38 (21.3)	3 (17.6)	1.00

Past history of hyperglycemic emergencies, n (%)	72 (40.4)	8 (47.1)	0.595
Co-morbidities, n (%)	96 (53.9)	11 (64.7)	0.394
Type of co-morbidity, n (%)			
Hypertensive heart disease	84 (47.2)	9 (52.9)	0.650
Cerebrovascular accident	16 (9.0)	3 (17.7)	0.221
Chronic renal failure	20 (11.2)	1 (5.9)	0.700
Chronic liver disease	5 (2.8)	2 (11.8)	0.116
Malignancy	3 (1.7)	2 (11.8)	0.061
No of co-morbidities, n = 107 (%)			1.00
≤ 1	64 (66.7)	7 (63.6)	
> 1	32 (33.3)	4 (36.4)	
Type of HE			0.362
DKA	76 (42.7)	7 (41.2)	
HHS	38 (21.3)	6 (35.3)	
Mixed	64 (36.0)	4 (23.5)	
Random blood sugar, mmol/L			0.402
< 16.6	37 (20.8)	2 (11.8)	
16.7 – 33.2	93 (52.2)	8 (47.1)	
> 32.2	48 (27.0)	7 (41.1)	
Temperature, n (%)			0.274
Hypothermia (≤ 36.1^{0}C)	18 (10.1)	2 (11.8)	
Normothermia (36.2^{0}C – 37.2^{0}C)	88 (49.4)	5 (29.4)	
Fever (> 37.2^{0}C)	72 (40.5)	10 (58.8)	
GCS, n (%)			0.006
Mild	162 (91.0)	11 (64.7)	
Moderate	11 (6.2)	4 (23.5)	
Severe	5 (2.8)	2 (11.8)	
Blood pressure, n (%)			0.096
Hypotension	11 (6.2)	3 (17.6)	
Normotension	113 (63.5)	7 (41.2)	
Hypertension	54 (30.3)	7 (41.2)	
Tachycardia, n (%)	77 (43.3)	6 (35.3)	0.526
Tachypnoea, n (%)	82 (46.1)	9 (52.9)	0.587
Anemia, n (%)	143 (80.3)	14 (82.3)	1.00
Elevated urea, n (%)	54 (30.3)	8 (47.1)	0.157

WBC counts, n (%)			0.688
Leucopenia	24 (13.5)	3 (17.7)	
Normal	103 (57.9)	8 (47.1)	
Leucocytosis	51 (28.6)	6 (35.2)	
Serum sodium, n (%)			0.144
Hyponatremia	61 (34.3)	6 (35.3)	
Normonatremia	101 (56.7)	7 (41.2)	
Hypernatremia	16 (9.0)	4 (23.5)	
Serum potassium, n (%)			0.081
Hypokalemia	14 (7.9)	4 (23.5)	
Normokalemia	133 (74.7)	12 (70.6)	
Hyperkalemia	31 (17.4)	1 (5.9)	
Acidosis, n (%)	48 (27.0)	6 (35.3)	0.463
Elevated anion gap, n (%)	161 (90.4)	13 (76.5)	0.093
Hyperosmolarity, n (%)	26 (14.6)	5 (29.4)	0.111
Duration of hospital stay, n (%)			0.032
≤ 7 days	20 (11.2)	5 (29.4)	
> 7 days	158 (88.8)	12 (70.6)	

(HE = Hypertensive emergencies; DKA = Diabetic Keto Acidosis; MHE = Mixed Hyperglycemic Emergencies)

Table 5: Multivariate logistic regression of predictors of mortality in hyperglycemic emergencies

Characteristics	**Odds ratio**	**95% CI of Odds Ratio**	**P – value**
Age group, n (%)			
≤ 40	Reference		
41 – 64	9.1	0.56 – 146.9	0.120
≥ 65	18.9	0.93 – 383.4	0.056
Employment status, n (%)			
Unemployed	Reference		
Employed	6.1	0.77 – 48.2	0.087
Duration of Diabetes, years, n (%)			
< 5	Reference		
5 – 9	6.8	1. – 42.1	0.040
≥ 10	3.8	0.79 – 17.8	0.097

Co-morbidity, n (%)			
No	Reference		
Yes	0.82	0.18 – 3.6	0.790
GCS, n (%)			
Mild	Reference		
Moderate	4.6	0.73 – 29.2	0.103
Severe	10.2	1.03 – 101.6	0.047
Blood pressure, n (%)			
Hypotension	Reference		
Normotension	0.045	0.005 – 0.400	0.005
Hypertension	0.067	0.0070 – 0.644	0.019
Elevated urea, n (%)			
No	Reference		
Yes	0.80	0.20 – 3.4	0.768
Serum sodium, n (%)			
Hyponatremia	Reference	0.2 – 3.5	0.698
Normonatremia	0.73	0.07 – 27.7	0.803
Hypernatremia	1.4		
Serum potassium, n (%)			
Hypokalemia	Reference	0.015 – 0.66	
Normokalemia	0.1	0.002 – 0.83	0.017
Hyperkalemia	0.04		0.038
Hyperosmolarity, n (%)			
No	Reference		
Yes	1.05	0.07 – 16.1	0.970
Duration of hospital stay, n (%)			
≤ 7 days	Reference		
> 7 days	0.23	0.04 – 1.4	0.113

CI = Confidence Interval

4. Discussion

Hyperglycemic emergencies are increasingly common indications for hospital admissions in those living with DM. [2,4] In this study, 42.4% of the hospitalization in people living with DM was a result of HE. This is similar to the 40% reported by Ogbera *et al*,[37] and 46% reported by Oguejiofor *et al*[38] in tertiary health facilities in Nigeria; and 43.5% by Ekpebegh *et al*[39] in South Africa but higher than the 29.8% reported by Chijioke *et al*[40] and 11.8% by Ajayi *et al*.,[15] in other tertiary health facilities in Nigeria. Other studies in Nigeria reported higher prevalence in the range 76.9 – 83.0%.[41-43] These differences may have arisen due to the variations in operational definitions of HE in these studies. Diabetic Ketoacidosis was the commonest HE occurring in 42.6% of the admissions while MHE and HHS

accounted for 34.9% and 22.5% of HE respectively. This is in contrast with reports from other studies in Nigeria where HHS tend to predominate,[44-47] but similar to the reports of Desse *et al*,[48] and Ogbera *et al*.[19]

The overall mortality due to HE in this study was 8.7%. This is similar to the mortality range of 6.8% - 20.2% reported in similar studies across Africa [19, 39]. This underscores the need for more efforts towards diabetic education and management in this region.

The mean age of our study subjects was 53.6 ± 14.5 years, with majority between 41 – 64 years and 94.4% of all subjects having type 2 DM. This is in agreement with similar studies in Nigeria and the global trend where most type 2 DM occur in the fifth and sixth decades of life.[1,16] Furthermore, 54.9% of the subjects had at least one co-morbidity and hypertensive heart disease was the commonest. This is unsurprising given the fact that previous studies had documented higher cardiovascular risk among subjects living with DM compared to the general population.[49] In addition, diabetes is associated with cluster of metabolic risk factors including hypertension, dyslipidemia and central obesity.[50] This observation underscores the need for continuous surveillance and management of cardiovascular risk in this population.

Accurate and prompt diagnosis of HE is premised on the understanding of the signs and symptoms that constitute the syndrome. In our study, HE presented with diverse clinical and laboratory features. However, osmotic symptom was the commonest seen in 71.3%, and this was slightly higher in HHS compared to DKA and MHE. This could be the result of osmotic diuresis and the greater degree of dehydration that characterize HHS. Tachypnea was the commonest sign, present in 46.7%, and more in DKA (56.6%) compared to HHS (47.7%) and MHE (33.85%). This is expected in view of the profound ketosis that is usually associated with DKA which triggers hyperventilatory response to metabolic acidosis. There were varying degree of mental alteration in the subjects with HE, but the highest proportion of moderate-severe impairment was seen in the those with HHS. Reports from other studies have demonstrated similar alteration in mental status as characteristic of HHS, and this is believed to be the result of hyperosmolality.[2,20] Nonetheless, alteration in mental status in HHS usually resolves once osmolality returns to normal.

High anion metabolic acidosis was the commonest biochemical abnormality and this was profoundly more in DKA (98.8% vs. 81.8% vs. 82.3%, $p = 0.001$). This underscores the effect of insulin deficiency and the increase counterregulatory hormones in DKA with resultant lipolysis and unrestrained hepatic fatty acid oxidation to ketone bodies.[2]

Other clinical and biochemical presentations seen in this study were as described in previous studies.[2,4,17,19]

Infection, non-compliance to medication and dietary regimen; newly diagnosed DM, trauma, and CVA were the precipitating factors of HE in this study and this is similar to what has been previously documented.[19,48] The observation that diabetic hand and foot sepsis; UTI, other sepsis, pneumonia, malaria and cellulitis rank high among the people living with DM is of clinical importance, and efforts should be made by the managing physicians to routinely look out for these conditions as soon as individuals with HE present to the hospital.

In this study, duration of diabetes between 5-9 years, severe coma, hypotension and hypokalemia

were identified as the significant predictors of mortality among people living with DM and presenting with HE.

The authors recognize that the study has limitations. The classification of DM into type 1 or type 2 was purely based on epidemiology and clinical response to insulin or oral antidiabetic medications, as assessment of C-peptides or auto-antibodies were not routinely done in the study center, and so largely missing in almost all patients records. Nevertheless, the study proves that hyperglycemic emergencies are still common causes of hospital admission and mortality among people living with DM and it manifests with myriads of clinical and biochemical presentations. The study also identified some features that should alert managing physicians to suspect the possibility of HE. These features are osmotic symptom, tachypnoea and high anion metabolic acidosis. The study also identified the commonest precipitating factors. Further studies should include lower level health facilities where most patients access care and where expertise could be limited. This could give a better estimate of overall mortality from HE among persons living with DM.

References

1. International Diabetes Federation. *Diabetes Atlas*. 9th ed. Brussels, Belgium: International Diabetes Federation, 2019.
2. Kitabchi AE, Umpierrez GZ, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2009; 32 (7):1335-43. https://doi: 10.2337/dc09-9032
3. Goguen J, Gilbert J. Hyperglycemic emergencies in adults: diabetes Canada clinical practice guideline expert committee *Can J Diabetes* 2018; (42), S109 – S114. https://doi.org/10.1016/j.jcjd.2017.10.013
4. Kitbachi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2006; 29 (12):2739-48. https://doi.org/10.2337/dc06-9916
5. Savage MW, Dhatariya KK, Kilvert A, Rayman G, Rees JA, Courtney CH, Hilton L, at al, for the Joint British Diabetes Societies. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabetic Med*. 2011; 28 (5):508–15. https://doi:10.1111/j.1464-5491.2011.03246.x
6. Chiasson JL, Aris-Jilwan N, Belanger R et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *CMAJ* 2003; 168 (7):859 - 66
7. Kitbachi AE, Fisher JN, Murphy MB, Rumbak MJ. Diabetic ketoacidosis and the hyperglycemic hyperosmolar nonketotic state. In Joslin's Diabetes mellitus. 13th ed. Kahn CR, Weir GC, Eds. Philadelphia, Lea & Febiger, 1994, p.738 – 770
8. Chung ST, Perue GG, Johnson A, Younger N, Hoo CS, Pascoe RW, Bayne MS. Predictors of hyperglycemic crises and their associated mortality in Jamaica. *Diabetes Res Clin Pract* 2006; 73 (2): 184-190. DOI: 10.1016/j.diabres.2006.01.004
9. Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: A historic review of the clinical presentation, diagnosis, and treatment. *Diabetes Care* 2014; 37 (11):3124-31. DOI: 10.2337/dc14-0984.
10. Fourtner SH, Weinzimer SA, Levitt Katz LE. Hyperglycemia, hyperosmolar non-ketotic syndrome in children with Type 2 diabetes. *Paediatr Diabetes* 2005; 6 (3):129-35. DOI: 10.1111/j.1399-543X.2005.00113.x

11. Huang CC, Kuo SC, Chien TW, Lin HJ, Guo HR, Chen WL, Chang SH et al. Predicting the hyperglycemic crises death (PHD) score: a new decision rule for emergency and critical care. *Am J Emerg Med* 2013; 31 (5): 830 - 834. DOI: 10.1016/j.ajem.2013.02.010
12. Dhatariya KK, Parsekar K, Skedgel C, Datta V, Hill P, Fordham R. The cost of treating diabetic ketoacidosis in an adolescent population in the UK: a national survey of hospital resource use. *Diabet Med.* 2019 Aug;36(8):982–987; DOI:10.1111/dme.13893.
13. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.
14. Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality - United States, 2000-2014. *MMWR Morb Mortal Wkly Rep* 2018; 67 (12):362-365. DOI: 10.15585/mmwr.mm6712a3
15. Ajayi EA, Ajayi AO. Pattern and outcome of diabetic admissions at a federal medical center: A 5-year review. *Annals of African Medicine* 2009; 8 (4): 271-275 DOI: 10.4103/1596-3519.59584
16. Adeloye D, Ige JO, Aderemi AV, Adeleye N, Amoo EO, Auta A, Oni G. Estimating the prevalence, hospitalization and mortality from type 2 diabetes mellitus in Nigeria: a systematic review and meta-analysis. *BMJ Open* 2017; 7: e015424. Doi:10.1136/bmjopen-2016-015424
17. Anumah F, Ohwovoriole A. Serum biochemistry in Nigerians with hyperglycemic emergencies. *Ethn Dis.* 2008;18(1):26-30.
18. Okoro EO, Yusuf M, Salawu HO and Oyejola BA. Outcome of diabetic hyperglycaemic emergencies in a Nigerian cohort. *Chinese Journal of Medicine* 2007; 2(2):77-82
19. Ogbera OA, Awobusuyi J, Unachukwu C, Fasanmade O. Clinical features, predictive factors and outcome of hyperglycemic emergencies in a developing country. *BMC Endocrine Disorders* 2009, 9:9. Doi:10.1186/1472-6823-9-9.
20. Kitbachi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001; 24 (1): 131-153. https://doi.org/10.2337/diacare.24.1.131
21. Wachtel TJ, Tetu-Mouradjian LM, Goldman DL, Ellis SE, O'Sullivan PS. Hyperosmolarity and acidosis in diabetes mellitus: a three-year experience in Rhode Island. *J Gen Intern Med* 1991; 6 (6): 495-502. DOI: 10.1007/BF02598216.
22. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6-degree Fahrenheit, the upper limit of normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA* 1992; 268 (12):1578—80.
23. World Health Organization. Thermal protection of the newborn: A practical guide. *World Health Organization*; Geneva: 1997. Report No.: WHO/RHT/MSM/97.2.
24. Gopinathannair R, Sullivan RM, Olshansky B. Slower heart rates for healthy hearts: time to redefine tachycardia? *Circ Arrythm Electrophysiol.* 2008; 1:321–3. doi: 10.1161/CIRCEP.108.835264.
25. Palatini P. Need for a revision of the normal limits of resting heart rate. *Hypertension* 1999; 33:622–5. doi: 10.1161/01.HYP.33.2.622.
26. Cretikos MA, Bellomo R, Hillman K, Chen J, Finfer S, Flabouris A. Respiratory rate: the neglected vital sign. *Med J Aust* 2018; 188: 657- 659. doi: 10.5694/j.1326-

5377.2008.tb01825.x
27. Petridou ET, Antonopoulos CN. (2017). *Injury Epidemiology. International Encyclopedia of Public Health, 258–274*. doi:10.1016/b978-0-12-803678-5.00233-2
28. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A et al. 2020 International Society of hypertension Global Hypertension Practice Guidelines. *Hypertension* 2020; 75 (6):00-00. Doi:10.1161/HYPERTENSIONAHA.120.15026
29. Worthley LI. Shock: A Review of Pathophysiology and management. Part 1. *Crit Care Resusc* 2000; 2 (1): 55 – 65.
30. Sterns RH. Disorders of plasma sodium – causes, consequences, and correction. *N Engl J Med* 2015; 372: 55-65. DOI:10.1056/NEJMra1404489
31. Gumz ML, Rabinowitz L, Wingo CS. An Integrated view of potassium homeostasis. *N Engl J Med* 2015; 373: 60 – 72. DOI: 10.1056/NEJMra1313341.
32. Kraut JA, Madias NE. Serum Anion Gap: Its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol* 2007; 2: 162–174, 2007. doi: 10.2215/CJN.03020906
33. Arieff AI, Carroll HJ. Hyperosmolar nonketotic coma with hyperglycemia: abnormalities of lipids and carbohydrate metabolism. *Metabolism* 1971; 20 (6):529-538. https://doi.org/10.1016/0026-0495(71)90001-1
34. Hoffman R, Benz EJ Jr, Silberstein LE, Heslop H, Weitz J, Anastasi J. *Hematology: Basic Principles and Practice*. 6th ed. Philadelphia, Pa.: Elsevier/Saunders; 2013: Table 164-20.
35. World Health Organization. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015.
36. Stoner GD. Hyperosmolar hyperglycemic state. *Am Fam Physician*. 2005;71(9):1723-1730.
37. Ogbera OA, Chinenye S, Onyekwere A, Fasanmade O. Prognostic indices of diabetes mortality. *Ethn Dis* 2007; 17 (4): 721-5.
38. Oguejiofor O, Odenigbo C, Onwukwe C. Diabetes in Nigeria: Impact, Challenges, Future Directions. *Endocrinol Metab Synd* 2014; 3(2). DOI: 10.4172/2161-1017.1000130
39. Ekpebegh CO, Long-Mbenza B, Akinrinmade A, Blanco-Blanco E, Badri M, Levitt NS. Hyperglycemic crises in the Eastern Cape province of South Africa: High mortality and association of hyperosmolar ketoacidosis with a new diagnosis of diabetes. *S Afr Med J* 2010; 822-826. doi:10.7196/samj.4319
40. Chijioke A, Adamu AN, Makusidi AM. Mortality patterns among type 2 diabetes mellitus patients in Ilorin, Nigeria. *JEMDSA* 2010; 15(2):79-82
41. Ojobi JE, Dunga J, Ogiator MO, Mbaave P, Bello RN. Indications and outcome of admission of diabetic patients into the medical wards in a Nigerian tertiary hospital-A 2-year review. *Jos Journal of Med* 2017; 11(2): 53-8
42. Nkpozi MO, Ezeani IU, Korubo IF, Chinenye S, Chapp-Jumbo A. Outcome of hyperglycemic emergencies in a tertiary hospital, South East, Nigeria. *Sahel Med J* 2019; 22:47-54. DOI: 10.4103/smj.smj_71_17
43. Uloko AE, Adeniyi AF, Abubakar LY, Yusuf SM, Abdu A, Gezewa ID, Uloko AT. Pattern of diabetes admissions in a Northern Nigerian tertiary center. *Nig End Prac* 2013; 7(1): 15-20
44. Umoh VA, Out AA, Enang OE, Okereke QO, Essien O, Ukpe I. The pattern of diabetic admissions in UCTH Calabar, South Eastern Nigeria: a five-year review. *Nig Health J* 2012; 12 (1):7-11.
45. Edo AE. Clinical profile and outcomes of

adult patients with hyperglycemic emergencies managed at a tertiary care hospital in Nigeria. *Nig Med J* 2012; 53(39. 121-125. DOI: 10.4103/0300-1652.104378

46. Ezeani UI, Eregie A, Edo AE. Pattern of presentation, socio-demographic and clinical characteristics of patients presenting with hyperglycemic emergencies in a Nigerian Hospital. *Pioneer Med J* 2013; 3 (5):1-15
47. Olugbemide O, Bankole I, Akhuemokhan K, Adunbiola P. Clinical profile and outcome of hyperglycemic emergencies at a rural hospital in southern Nigeria. *Afr J of Dia Med* 2017; 25 (2): 16-18
48. Desse TA, Eshetie TC, Gudina EK. Predictors and treatment outcome of hyperglycemic emergencies at Jimma University Specialized Hospital, southwest Ethiopia. *BMC Res Notes* 2015; 8:553
49. Fox CS. Cardiovascular Disease Risk Factors, Type 2 Diabetes Mellitus, and the Framingham Heart Study. *Trends Cardiovasc Med.* 2010; 20 (3): 90-95.
50. Ginsberg HN, MacCallum PR. The obesity, metabolic syndrome, and Type 2 diabetes mellitus pandemic: Part 1. Increased cardiovascular disease risk and the importance of atherogenic dyslipidemia in persons with the metabolic syndrome and type 2 diabetes mellitus. *J Cardiometab Syndr.* 2009; 4: 113-119.

Citation: This article should be cited as: Bello-Ovosi, BO, Ovosi, JO, Bansi, OK. Hyperglycemic Emergencies in a Tertiary Health Facility: Clinical Presentation and Predictors of Mortality. Afr. J. Trop. Med. & Biomed. Res. 2022; 5(2): 6-23

Intensity of Urinary Schistosomiasis and Prevalence of Urinary Tract Pathology Among Primary School Pupils in Delta State, South-south, Nigeria

Mbagwu Nkemjika E[1], Ezeonwu BU[1], Agabi JO[1], Okolo Selina N[2]

Abstract

Background: The urinary tract pathology (UTP) of urinary schistosomiasis is a common complication of the infection caused by inflammatory reactions mainly against the deposited egg antigens around the urinary tract and it is a disease of major public health importance.

Objective: The aim of this study was to determine the correlation between the intensity of urinary schistosomiasis and the prevalence of its UTP among primary school pupils in Ndokwa-East Local Government Area (NELGA) of Delta State, South-south Nigeria.

Method: This study was a cross sectional descriptive study of primary school children aged 5-15 years in Ndokwa-East Local Government Area (NELGA) of Delta State. Urine microscopy was used to identify infected primary school pupils. The intensity of infection was classified using egg count according to World Health Organization (WHO) standard, after which they participated in an ultrasound examination, using WHO guideline for schistosomiasis morbidity.

Result: Among the infected subjects, 87.5% of those with severe infection had bladder wall pathology, while 71.4% of those with mild infection had bladder wall pathology (FET, p-value = 0.613). Additionally, 12.5% of those with severe infection as against 7.1% of those with mild infection had hydroureter (FET, p-value = 1.000), while 37.5% of those with severe infection as against 42.9% of those with mild infection had hydronephrosis (FET, p-value = 1.000).

Conclusion: The prevalence and severity of UTP in this study had no significant relationship with the intensity of infection.

Key Words: Urinary schistosomiasis, Urinary tract pathology, Intensity of infection, NELGA

[1]Department of Paediatrics, Federal Medical Centre, Asaba, Delta state, Nigeria. nkemjikambagwu@gmail.com +2348160853429
[1]Department of Paediatrics, Federal Medical Centre, Asaba, Delta state, Nigeria. Uzomavin2013@gmail.com +2348033257313
[1]Department of Radiology, Federal Medical Centre, Asaba, Delta state, Nigeria. triumphantjossy@yahoo.com +2348063273176
[2]Department of Paediatrics, Jos University Teaching Hospital, Jos, Plateau State, Nigeria. selineokolo@yahoo.com +2348037176960

INTRODUCTION

Schistosomiasis is an immunologic disease,[1,2,3] and the pathogenesis of acute, sub-acute, and chronic schistosomiasis involve immunologic mechanisms.1 The acute phase coincides with the invasion and migratory stages of the parasite life cycle.1 The sub-acute phase coincides mainly with granuloma formations in the bladder, lower ureters, seminal vesicles, prostate, female genital tracts, etcetera, depending on the quantity of schistosoma eggs and where they are deposited.1 The granuloma coalesce to form tubercles, nodules and masses that often ulcerate, giving rise to dysuria, hematuria, and proteinuria. 1 The masses can also obstruct urinary outflow, depending on their location, leading to hydronephrosis and hydroureter.1 Building up of

back pressure from the obstruction can lead to renal damage, depending on the severity.1 The chronic phase coincides with the period where antigen-antibody immune complexes are formed and deposited in the kidney, leading to proliferative glomerulonephritis. Oncogenic alterations resulting from error-prone repair of modified DNA (from schistosome egg-derived estrogen-like molecules and their metabolites reacting covalently with DNA bases), leading to urogenital carcinomas occur in the chronic phase too. 4 The prevalence of urinary schistosomiasis has remained relatively high in Ndokwa-East Local Government Area (NELGA) of Delta State and its Urinary Tract Pathology (UTP) is a disease of public health importance.5 However, there is paucity of data on the influence of the intensity of infection on the UTP of urinary schistosomiasis in NELGA of Delta State. This study therefore helped in addressing the above knowledge gap.

SUBJECTS AND METHODS

The study was conducted in the selected primary schools in Ndokwa East LGA of Delta State. It was a cross sectional descriptive study of primary school children aged 5-15 years in Ndokwa-East Local Government Area (NELGA) of Delta State, to determine the relationship between the severity of urinary tract ultrasonographic abnormalities among primary school children with urinary schistosomiasis and intensity of infection. Subjects' recruitment was by multistage, stratified sampling method. The wards and the primary schools were selected by simple random sampling method. Urine microscopy (urine centrifugation-sedimentation method of diagnosis) was used to separate infected and uninfected primary school pupils. The schistosoma eggs identified during the urine microscopy were counted twice (to minimize errors) and recorded as number of eggs per 10millilitres of urine (EP10ml) and graded according to World Health Organization (WHO) standard; <50 eggs/10 ml urine considered as mild infection, and ≥50 eggs/10 ml of urine as severe infection. 3 6 This was carried by a laboratory scientist who had undergone further training on parasitology, to ensure accuracy. All the infected subjects proceeded to the next stage of the study.

The infected pupils were scanned in the morning. The kidneys, the ureters, and the bladder of all the subjects were scanned using a 3.5Mhz curvilinear array transducer of a logic V5 ultrasound machine (GE Medical systems[CHINA] CO LTD, 2016), by a Consultant Radiologist, to minimize error. The radiologist had no knowledge of the intensity of infection of the subjects to minimize bias as well.

The kidneys were assessed in the longitudinal and transverse axis for pathologies of the renal parenchymal and pelvi-calyceal collecting systems. The abnormalities were classified and scored according to World Health Organization (WHO) guideline for schistosomiasis morbidity. The pathological lesions were classified into those affecting the bladder and those affecting the upper urinary tract (ureter and kidneys). For the bladder pathologies, the scores were given as follows; a wall irregularity with thickening up to 5mm is scored 1, and 2 if multifocal. A focal bladder wall thickening greater than 5mm was given a score of 1, and a score of 2 if multifocal. A mass considered as a localized thickening of the bladder wall, protruding into the lumen (> 10mm), was given a score of 2 when single and a score of n+2 for multiple masses (n = number of masses). Pseudo polyps, defined as outgrowths of the wall, attached by slender bases (narrower than the mass), were scored like the masses. Each lesion in the wall was scored only once, in one category

only. 7 Hydroureter was given a score of 3 when moderately dilated (the ureter being visualized at the proximal and/or distal third), and 4 when grossly dilated (the ureter being dilated more than is required for mere visualization). Hydronephrosis was given a score of 6 if dilated with conserved parenchyma (distance between renal pelvis and capsule being > 1cm), and a score of 8 if severely dilated with compression/absence of parenchyma (distance between renal pelvis and capsule being < 1cm). Urinary tract lesions not meeting the above criteria were given scores of 0. 7 Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22. Intensity of infection and prevalence/severity of urinary tract abnormality were treated as categorical variables and expressed using frequency tables and charts. The significance of association between the prevalence of UTP and intensity of infection were tested using chi-square test and Fisher's exact test when indicated. The level of significance was set at a p-value of less than 0.05.

Ethical Consideration

Ethical clearance was obtained from the Ethics Committee, FMC Asaba. Written permissions were obtained from the State Ministry of Basic and Secondary Education, and the Local Government Chairman. Verbal permission was obtained from the community leaders. Written informed consent were obtained from the parents/caregivers of the study participants and written assent were obtained from the participants aged ≥ 7years

RESULTS

General characteristics of the study population

There were 22 infected study participants who completed the study. There were 13 males (59.1%) and 9 females (40.9%), giving a ratio of 1.4:1. They all belonged to the lower socio-economic status. The mean (SD) of weight, height, and body mass index (BMI) of the subjects were 26.3kg (11.1), 123.4cm (16.3), and 16.6kg/m^2 (3.4) respectively.

Among the infected subjects that completed the study, 77.3% (17/22) had UTP using ultrasonography.

Intensity of the US infection in the subjects

Fourteen out of the 22 infected subjects (63.6%) that completed the study had mild infection, while the rest had severe infection

Prevalence of UTP among the study participants

Seventeen (77.3%) out of the 22 infected pupils studied, had at least one abnormality of the bladder wall such as bladder mass, increased bladder wall thickness, abnormal bladder wall shape, and bladder wall irregularity. Two (9.1%) out of the 22 infected pupils had hydroureter, and 9 (40.9%) out of the 22 infected pupils had hydronephrosis of at least one kidney.

Relationship/correlation between the intensity of infection and prevalence of urinary tract pathologies.

The intensity of infection had no significant relationship with the prevalence of the urinary tract pathologies as shown in table I.

TABLE I: Relationship between intensity of infection and prevalence of UTP

Parameter		Intensity of infection		p-value
		Mild infection (N=14)	Severe infection(N=8)	
		n (%)	n (%)	
Abnormality of the bladder	Yes	10 (71.4)	7 (87.5)	0.613
	No	4 (28.6)	1 (12.5)	
Hydroureter	Yes	1 (7.1)	1 (12.5)	1.000
	No	13 (92.9)	7 (87.5)	
Hydronephrosis	Yes	6 (42.9)	3 (37.5)	1.000
	No	8 (57.1)	5 (62.5)	

FET = Fisher's Exact Test

Relationship between the Intensity of infection and severity of Urinary Tract Pathology of Urinary Schistosomiasis.

There was no significant relationship between the intensity of infection and severity of UTP as shown in Table II.

TABLE II: Relationship between intensity of infection and severity of UTP

Parameter		Intensity of infection		FET	p-value
		Mild infection (N= 10) n (%)	Severe infection (N= 7) n (%)		
Irregularity of the bladder wall	Normal	7 (70.0)	5 (71.4)	-	1.000
	Focal irregularity	1 (10.0)	1 (14.3)		
	Multifocal irregularity	2 (20.0)	1 (14.3)		
Thickening of the Bladder wall	No thickening	4 (40.0)	4 (57.1)	-	0.647
	Focal thickening	2 (20.0)	0 (0.0)		
	Multifocal thickening	4 (40.0)	3 (42.9)		
Bladder wall mass	No mass	9 (90.0)	5 (71.4)	-	0.537
	Multiple masses	1 (10.0)	2 (28.6)		
Bladder wall shape	Normal shape	5 (50.0)	2 (28.6)	-	0.354
	Abnormal shape	5 (50.0)	5 (71.4)		
Severity of the hydronephrosis	Unilateral mod hydroneph	2 (33.3)	2 (66.7)	-	1.000
	Bilateral mod hydroneph	3 (50.0)	1 (33.3)		
	Severe hydronephrosis	1 (16.7)	0 (0.0)		

mod = *moderate,* hydroneph = *hydronephrosis,* FET = *Fisher's Exact Test*

DISCUSSION

The prevalence and severity of UTP in this study had no significant relationship with the intensity of infection. Similar to this finding, King et al8 and Onile et al; 9 reported that subjects with bladder pathologies, could have mild or severe schistosomiasis infection. The finding is however at variance with those of Vester et al, 10 Ekwunife et al,11 Nmorsi et al,12 and Sacko et al; 13 who all reported that UTP of urinary schistosomiasis were associated with increasing egg output.10[11,12,13] A number of factors may play a role in the differences. Genetic factors for instance, as suggested by Kouriba et al14 in Mali, may play a role in the similarity between this index study and the studies by King et al8 and Onile et al. 9 It may be that majority of the subjects with UTP were immunologically naïve, and so, mounted a vigorous inflammatory response to any infection, be it mild or heavy infection;[14] resulting in UTP. It may also be that acquired immunity developed earlier in areas of high exposures, and this acquired immunity modulated the host immune response to the antigen of schistosoma eggs, to the development of UTP, especially in heavily infected subjects. This is as reported by Joseph et al15 in 2004, and Woolhouse et al16 in 1999.

CONCLUSION

The prevalence and severity of UTP in this study had no significant relationship with the intensity of infection. Therefore, the final thought on the influence of severity of infection on the development of UTP from this study is that intensity of schistosomiasis infection alone may not affect the development of UTP of schistosomiasis. This influence may be altered probably by genetic make-up of the parasite, and the hosts' immune response.

REFERENCES

1. Barsoum RS, Esmat G, El-Baz T. Human Schistosomiasis: Clinical Perspective: Review. J Adv Res. 2013;4(5):433-444. doi:10.1016/j.jare.2013.01.005
2. Ahmed SH. Schistosomiasis. In: Medscape.Com. Available at http://www.emedicine.medscape.com/article228392-overview. Accessed 10/11/2016.
3. King CH. Schistosomiasis. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF (ed) Nelson Textbook of Pediatrics. 18th Edition. Saunders Elsevier Philadelphia. 2007: 1508-1510.
4. Tuffour I, Ayi I, Gwira TM, Dumashie E, Ashong Y, Appiah-Opong R. Schistosoma egg antigen induces oncogenic alterations in human prostate cells. Anal Cell Pathol. 2018;Article ID:1-10. doi:10.1155/2018/4675380
5. Ekwunife CA, Agbor VO, Ozumba AN, Eneanya CI Ukaga CN. Prevalence of urinary schistosomiasis in Iyede-Ame Community and environ in Ndokwa East Local Government Area , Delta State , Nigeria. Niger J Parasitol. 2009;30:27-31.
6. Schistosomiasis. http://www.cdc.gov/parasites/schistosomiasis/disease.html.
7. Richter J, Campange G, Hatz G, Berquist NR, Jenkins JM. Ultrasound in Schistosomiasis: A Practical guide to the standardized use of ultrasonography for the assessment of Schistosomiasis-related Morbidity. World Heal Organ. 1996;55:19-25. doi:10.1111/j.1365-2893.2009.01252.x
8. King CH, Keating CE, Muruka JF,Ouma JH, Houser H, Siongok TK, et al. Urinary tract morbidity in schistosomiasis haematobia: Associations with age and intensity of infection in an endemic area of Coast Province, Kenya. Am J Trop Med Hyg. 1988;39:361-368. doi:10.4269/ajtmh.1988.39.361
9. Onile OS, Awobode HO, Oladele VS, Agunloye AM, Anumudu CI. Detection of

urinary tract pathology in some schistosoma haematobium infected nigerian adults. J Trop Med. 2016;2016. doi:10.1155/2016/5405207

10. Vester U, Kardorff R, Traoré M, Traore HA, Fongoro S, Juchem C, et al. Urinary tract morbidity due to Schistosoma haematobium infection in mali. Kidney Int. 1997;52(2):478-481. doi:10.1038/ki.1997.356
11. Ekwunife CA, Okafor FC, Nwaorgu OC. Ultrasonographic screening of urinary schistosomiasis infected patients in Agulu community, Anambra state, southeast Nigeria. Int Arch Med. 2009;2:34. doi:10.1186/1755-7682-2-34
12. Nmorsi OPG, Ukwandu NCD, Ogoinja S, Blackie HOT, Odike MAC. Urinary tract pathology in Schistosoma haematobium infected rural Nigerians. Southeast Asian J Trop Med Public Health. 2007;38(1):32-37.
13. Sacko M, Magnussen P, Keita AD, Traore MS, Landoure A, Doucoure A, et al. Impact of Schistosoma haematobium infection on urinary tract pathology, nutritional status and anaemia in school-aged children in two different endemic areas of the Niger River Basin, Mali. Acta Trop. 2011. doi:10.1016/j.actatropica.2010.12.009
14. Kouriba B, Traore HA, Dabo A, Sangare L, Guindo H, Keita AS, et al. Urinary disease in 2 Dogon populations with different exposure to Schistosoma haematobium infection: progression of bladder and kidney diseases in children and adults. J Infect Dis. 2005;192:2152-2159. doi:10.1 086/498214
15. Joseph S, Jones FM, Walter K, Fulford AJ, Kimani G, Mwatha JK, et al. Increases in human T helper 2 cytokine responses to Schistosoma mansoni worm and worm-tegument antigens are induced by treatment with praziquantel. J Infect Dis. 2004;190:835-842. doi:10.1086/422604
16. Woolhouse MEJ, Hagan P. Seeking the ghost of worms past. Nat Med. 1999:1225-1227. doi:10.1038/15169

Citation: This article should be cited as: Mbagwu NE, Ezeonwu BU, Agabi JO, Okolo SN. Intensity of Urinary Schistosomiasis and Prevalence of Urinary Tract Pathology among Primary School Pupils in Delta State, South-south, Nigeria. Afr. J. Trop. Med. & Biomed. Res. 2022; 5(2): 24-29

Assessment Of Haematological And Antioxidants Changes In Male Albino Wistar Rats Treated With Tramadol

Ojieh Anthony Emeka[1], Ossai Nduka Richard[1], Nwogueze BC[2]

Abstract

Introduction

Illicit drug use disorders are a major public health burden that contributes significantly to the global burden of disease and tramadol is one of the most common illicit psychoactive substances being abused especially amongst the young adults. This research aims to assess the haematological and antioxidants activities of male wistar rats treated with tramadol.

Materials and Methods

Thirty adult male Wistar rats weighing 120-180 g were selected for the study and was randomized into 6 groups. Group 1 was not treated within the period of the study before sacrificing, Group 2 to 5 received 30 mg/kg body weight of tramadol for 7, 14, 21 and 42 days respectively while treatment for group 6 was withdrawn for 3 weeks after 21 days treatment period before sacrificing. The animal's Brain, Liver, kidney and Testis were excised for biochemical analysis. Generated data were analyzed using SPSS package and results expressed as mean ± SEM.

Results

Results obtained showed significant decrease in the haemtololgical parameters as well as in the WBC count, Catalase, SOD and Glutathione activities in the chronic tramadol-treated rats when compared to the normal control at $p<0.05$. This study also revealed that chronic tramadol use increases the level of MDA significantly when compared with the non-treated group.

Conclusion

Tramadol consumption lowers RBC count, haemoglobin level, PCV, platelet count, WBC count, CAT, SOD, and GSH activities while significantly raising MDA levels. Therefore tramadol should only be used under medical supervision and only on prescription, avoiding indiscriminate and long-term.

[1].Department of Human Physiology, Faculty of Basic Medical Sciences, Delta State University, Abraka, Delta State, Nigeria.
[2].Department of Human Physiology, College of Health Sciences, Evangel University, Akaeze, Ebonyi State Nigeria.

Corresponding Author: Ossai, Nduka Richard (Department of Human Physiology, Delta State University, Abraka, Nigeria)

1.0 INTRODUCTION

Tramadol, a centrally acting analgesic agent with activity at μ-opioid, adrenergic and 5-hydroxytryptamine (5-HT) receptors (18, 25), has recently become a cause of major addiction in Nigeria especially amongst young adult, and of recent, many reports confirm the scourge of tramadol addiction of which many health workers were unaware of the scale of its non-medical use and abuse (22). The central role of liver and kidney in drug metabolism predisposes them to toxic injury, however, tramadol has been heralded as a non-abusable replacement option for many of the existing opiate painkillers, and the potential for abuse naturally does exist. If a user

takes tramadol repeatedly over a period and develops a tolerance for the drug, an overdose may occur when that user takes more than normal to achieve the desired effect; hence, tramadol overdoses had been reported to be very serious and can cause neurological toxicity, Respiratory failure, Serotonin syndrome and Mild, moderate or even severe cardiovascular disruption (19, 21). Although fatal intoxications of tramadol are rare and appear to be associated with large overdoses and co-ingestion of other drugs and /or alcohol (21). Symptoms of overdose may include; depression, addiction and seizures, change in consciousness, decreased awareness or responsiveness, difficulty with breathing, lack of muscle tone, light-headedness, loss of consciousness, pinpointed pupils of the eyes, severe sleepiness, slow or irregular heartbeat and unusual tiredness (20) With the current abuse of tramadol in Nigeria, this study therefore aim to access the haematological and antioxidant properties in albino wistar rats treated with tramadol.

2.0 MATERIALS AND METHOD

2.1 Chemicals and Drugs

Tramadol was purchased from Demeck pharmaceutical, Obiaruku, Delta State, Nigeria, All the chemicals and drugs used were of analytical grade

2.2. Experimental Animal

Thirty (30) adult male Wistar rats were purchased for this research at the Faculty of Basic Medical Sciences Animal Farm, Delta State University, Abraka, Nigeria, and housed in metabolic cages. They were kept on the animal feed growers' daily mash diet, a product of Top Feed in Sapele, Delta State. Feed components include: 17.0 percent protein, 4.5 percent min. fat, 0.96 percent min. calcium, 3.92 percent usable min. phosphorus, and 2450kcal energy and water ad libitum.

2.3 Ethical Consideration

The Research, Ethics and Grants Committee of the Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria, reviewed and approved the protocol for this study, and the experiment was performed in accordance with the ethical guidelines for the care and use of animals as laid down Helsinki, 1964 (51).

2.4 Drugs Preparation and Administration

300 g of tramadol was dissolved in 50 ml of water and was administered orally to the rats acceding to their body weight.

2.5 Experimental Design:

Group 1 (n - 5) – Control Group Wister Rats were not treated within the period of the study before sacrificing.

Group 2 (n - 5) – Received 30 mg/kg body weight of tramadol for 7 days and was sacrificing.

Group 3 (n - 5) – Received 30 mg/kg body weight of tramadol for 14 days and was sacrificing.

Group 4 (n - 5) – Received 30 mg/kg body weight of tramadol for 21 days and was sacrificing.

Group 5 (n - 5) – Received 30 mg/kg body weight of tramadol for 42 days and was sacrificing.

Group 6 (n - 5) –Withdrawn for 3 weeks after receiving tramadol 30 mg/kg for 21 days before sacrificing

2.6 Sample Collection

Each rat was sacrificed by cervical dislocation and was placed on its dorsal surface, a laparotomy was carried out to reveal the internal organs, and blood was collected by cardiac puncture, using 5ml syringes and 23G needle into blood sample

containers and centrifuged for 10 minutes at a rate of 4000 rpm, and serum was collected and stored in blood sample containers.. The brain, liver, testis and kidney was harvested for biochemical analysis.

2.7 Biochemical Analysis

Biochemical analysis was carried out on the samples collected as follows;

2.7.1 Determination of Haematological parameters

Haematological parameters were measured using automated cell counter (Coulter Electronics, Luton, Bedfordshine, UK) having standard calibrations in line with the instructions of the manufacturer. Parameters measured were: RBC count, platelet count, PCV and Hb concentration.

2.7.2 Determination of Total and Differential White Blood Cell Count.

Total and differential White blood cell count was calculated using manual cell counting chamber with Neubaurer Chamber according to Dhurba (50)

2.7.3 Determination of Catalase Activity

The activity of catalase was determined in the tissue homogenates by the method adopted by Viviam (14) and Ossai *et al.* (17)

2.7.4 Determination of SOD Activity

The activity of SOD in the tissue homogenates was estimated spectrophotometrically using the method of Misra and Fredorich (15) and adopted by Ossai *et al.* (17)

2.7.5 Determination of GSH Activity

The reduced glutathione was estimated in serum and tissue homogenates using the method of Ellman (12) and adopted by Beulter *et al.* (13)

2.7.6 Determination of MDA Activity

A breakdown product of lipid peroxidation thiobarbitoric acid reactive substance (TBARS) was measured in the tissue homogenates by the method of Gutteridge and Wilkins (16) and adopted by Ossai *et al.* (17)

2.8 Statistical analysis

The data were analyzed by comparing the values for individual controls for different treatment groups and the results were expressed as mean values ± standard mean error (mean ± SEM). Using the student's t-test, ANOVA variance analysis, and the results were considered significant at P-values of less than 0.05 ($P<0.05$) using SPSS version 23 software, significant differences between control and experimental groups were measured.

3.0 RESULTS

Table 1: Effects of Tramadol consumption on relative organ weight of male Wistar rat

Group	Brain Weight	Liver Weight	Kidney Weight	Testis Weight
Group 1	.....	3.10±0.16	0.54±0.06	1.03±0.11
Group 2	0.79±0.11	3.21±0.06	0.63±0.03	1.55±0.09
Group 3	1.20±0.08	3.09±0.23	0.53±0.12	0.84±0.06
Group 4	1.16±0.09	2.55±0.08	0.30±0.02	0.59±0.07
Group 5	0.86±0.09	3.23±0.11	0.69±0.08	1.36±0.13
Group 6	1.36±20.48	2.93±0.07	0.69±0.03	1.32±0.19

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at P<0.05. [a]P<0.05 indicate significant increase and [b]P>0.05 indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 2: Outcome of Tramadol consumption on hematology in male Wistar rat

Group	RBC	HB	PCV	PLT
Group 1	9.90±0.50	15.43±0.69	41.20±1.39	360.40±33.96
Group 2	10.36±0.40	16.81±0.12	43.40±1.36	342.80±22.42
Group 3	10.55±0.45	16.23±1.07	44.40±3.41	334.60±63.95
Group 4	10.76±0.41	15.21±0.49	41.20±0.86	288.00±38.47
Group 5	10.23±0.47	16.27±0.60	42.20±0.92	390.40±9.89
Group 6	9.85±0.45	16.03±0.61	41.40±1.25	375.20±15.02

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at P<0.05. [a]P<0.05 indicate significant increase and [b]P>0.05 indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 3: Outcome of Tramadol consumption on total and differential count of WBC in male Wistar rat

Groups	WBC	LYM	MID	GRA	LYM%	MID%	GRA%
1	10.87±0.87	7.11±0.67	1.70±0.24	2.82±0.30	67.87±3.82	14.16±1.57	24.28±2.91
2	9.86±0.85	6.51±0.67	1.40±0.12	2.31±0.44	67.43±4.17	14.76±1.71	24.06±3.85
3	10.23±1.02	7.48±0.73	1.37±0.20	2.16±0.12	69.79±3.51	12.70±1.39	21.94±2.13
4	10.29±1.10	7.14±0.73	1.53±0.16	2.75±0.23	62.71±2.90	11.50±1.19	25.70±2.49
5	10.37±0.60	6.91±0.55	1.34±0.18	2.88±0.33	65.37±3.11	13.02±1.88	27.88±2.67
6	9.81±0.87	7.29±0.79	1.52±0.22	2.61±0.30	66.89±3.43	14.24±1.81	25.16±3.22

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at $P<0.05$. $^{a}P<0.05$ indicate significant increase and $^{b}P>0.05$ indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 4: Outcome of Tramadol consumption on Catalase Activates in male wistar rats

Group	CAT (U/mg protein)			
	Brain	**Testis**	**Kidney**	**Liver**
Group 1	$64.82±0.98^{a}$	$22.62±2.18^{a}$	$47.59±1.89^{a}$	$52.60±1.33^{a}$
Group 2	$53.88±3.76^{b}$	$26.82±1.26^{a}$	$43.92±2.51^{b}$	$49.43±1.47^{b}$
Group 3	$35.63±4.77^{b}$	$25.36±3.03^{a}$	$27.29±0.96^{c}$	$43.35±2.69^{b}$
Group 4	$31.62±0.98^{b}$	$29.88±2.01^{a}$	$27.90±1.37^{c}$	$41.80±3.16^{c}$
Group 5	$32.85±0.31^{b}$	$22.25±1.29^{a}$	$25.738±2.39^{c}$	$43.02±1.63^{c}$
Group 6	$22.79±2.18^{b}$	$21.31±1.29^{a}$	$20.39±1.04^{c}$	$44.09±3.50^{b}$

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at $P<0.05$. $^{a}P<0.05$ indicate significant increase and $^{b}P>0.05$ indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 5: Outcome of Tramadol consumption on SOD Activates in male wistar rats

Group	SOD (U/mg protein)			
	Brain	**Testis**	**Kidney**	**Liver**
Group 1	41.29±1.66[a]	40.64±6.10	48.09±1.87[a]	52.28±1.52[a]
Group 2	39.44±1.79[b]	35.99±5.49	41.81±3.40[b]	48.42±1.70[b]
Group 3	26.43±1.47[b]	30.21±.629	30.62±0.62[c]	39.09±1.25[c]
Group 4	33.40±0.70[b]	32.22±2.39	41.67±2.75[b]	43.16±1.60[c]
Group 5	36.11±2.51[b]	35.00±1.54	41.54±1.66[b]	46.33±3.33[b]
Group 6	34.65±2.29[b]	43.80±1.20	38.97±3.38[b]	47.27±2.95[b]

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at P<0.05. [a]P<0.05 indicate significant increase and [b]P>0.05 indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 6: Outcome of Tramadol consumption on GSH Activates in male wistar rats

Group	GSH (Unit/mg protein)			
	Brain	**Testis**	**Kidney**	**Liver**
Group 1	40.25±1.51	38.29±2.36	44.17±6.08	38.24±2.49
Group 2	49.12±3.88	32.13±1.93	51.86±2.57	52.36±12.94
Group 3	47.21±2.04	30.51±4.36	50.64±1.08	47.77±3.88
Group 4	41.10±3.04	35.21±3.22	48.30±1.70	36.53±2.18
Group 5	56.76±8.01	53.14±2.97	49.31±5.48	45.87±3.21
Group 6	52.31±1.20	45.16±1.82	47.04±7.31	45.07±4.81

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at P<0.05. [a]P<0.05 indicate significant increase and [b]P>0.05 indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 7: Outcome of Tramadol consumption on MDA Activates in male wistar rats

Group	MDA (Unit/mg protein)			
	Brain	**Testis**	**Kidney**	**Liver**
Group 1	1.03±0.23	0.93±0.44	1.03±0.23	1.08±0.17
Group 2	1.59±0.36	0.37±0.03	1.59±0.36	1.10±0.18
Group 3	2.10±0.94	0.39±0.09	2.10±0.94	1.84±0.77
Group 4	2.77±0.72	0.43±0.15	2.77±0.72	1.73±0.17
Group 5	2.34±0.47	0.79±0.18	2.34±0.48	2.03±0.62
Group 6	1.42±0.17	0.39±0.13	1.42±0.17	1.10±0.34

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at $P<0.05$. $^{a}P<0.05$ indicate significant increase and $^{b}P>0.05$ indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

4.0 DISCUSSION

Toxicity to tramadol can happen to those who take overdoses of the drug as a treatment of different types of pain as well as those who abuse it (23). Tramadol abuse had been known to be one of the most frequent health problems worldwide, and like other opioids, it is known to induce a decrease in plasma antioxidant levels, which may reflect a failure of the antioxidant defense mechanism against oxidative damage (24). It has been reported that abuse of tramadol causes antidepressant–like behaviour, impaired spatial memory, elevated 5–HT levels in the cerebral cortex and hippocampus, induced oxidative stress and apoptosis in brain tissue and deleteriously altered brain structure (37, 38). Withdrawal period has also been reported to show a reverse in antidepressant –like behavior, with no improvement of the spatial memory, and marked depletion of 5–HT as well as more improvement in antioxidants, apoptotic markers and incomplete recovery of brain histopathological alteration (39).

Tramadol in this study was given at a dose of 30mg/kg body weight orally (10% of oral LD_{50} of tramadol in rats) according to the study by "El-Gaafarawi (45)." Our findings in table 1 shows a relative organ weight gain in group 4 and 5 and no significant increase in group 2, 3 and 6 compared to control group 1. The significant weight gain after administration of tramadol (30mg/kg) could be as a result of tramadol effect which is believed to have caused little or no impact on user's eating habits. This is similar to a report by Mohammed and Mahmoud, (27) on body weight changes in control and tramadol-induced rats after administration of 30 and 60 mg/kg tramadol for 8 weeks but didn't induce significant changes

in the body weight.

Debate regarding the effect of tramadol on haematological parameters and bleeding profile exist in several literatures (28, 29, 30). In this present study, oral tramadol administration (30 mg/kg) to wistar rats within 6 weeks produce significant decrease in the haemtololgical parameters as shown in table 2. Haemoglobin c oncentration (Hb), packed cell volume (PCV), Red blood cell (RBC) and platelet counts were significantly decreased in all tramadol-treated group compared with controls. This results is in tandem with the findings of Nna *et al.* (31), Aldalou *et al.* (32), Udegbunam *et al.* (33), however, the significant decrease observed in Red Blood Cell (RBC) count, Packed Cell Volume (PCV) and hemoglobin (Hb) can be attributed to possible impairment of Haem-biosynthesis during erythropoiesis, as earlier reported by Nna *et al.* (31), blood loss due to serious gastrointestinal tract bleeding, invivo haemolysis (destruction of matured red blood cells) and poor iron absorption in the intestine which may have cause a decrease in oxygen supply to different tissues. Similar reports by Goeringer *et al.* (34), Mohammed *et al.* (35) and Abiodun *et al* (36) on hematological and biochemical changes in blood, liver and kidney tissues under the effect of tramadol treatment showed a decrease in RBC and Hb content. The decreased number of platelet count by tramadol in this study is in supports of pervious work by Abiodun and companion whose report on morphine administration resulted in thrombocytopenia (36).

In haematological studies conducted by Elyazji *et al.* (40), tramadol was found to increase WBC count, lymphocyte count and MCV, but decreased PCV, Hb, RBC count, MCH, MCHC and platelets count. Their finding showed signs of improvement of blood indices in the recovery periods after tramadol abstinence. Another study by Akhtardanesh *et al.* (41) in dogs showed that short-term injection of high doses of tramadol did not change haematological parameters significantly.

The free radicals and reactive oxygen species generated from the disruption of haematological parameters is a sign of toxicity or disease conditions (1, 2). In table 3 of this study, the effect of tramadol administration on white blood cell in male wistar rats was evaluated. Result shows a reduction in white blood cells count in all treated groups when compared to the control group wistar rats; this confirms the findings that tramadol administration in wistar rats causes a reduction in white blood cell count and this could suppress the immune system and possibly expose individuals to infectious disease (3, 4, 33). The disruptions in white blood cell observed in this study may be due to decreased population of unquenched free radicals caused by tramadol administration; a report which is in line with Owoade *et al.,* (36) findings.

Results from table 4 and 5 reveals a significant decrease in Catalase and superoxide dismutase activities of the brain, testis, kidney and liver tissues of male rats treated with tramadol, when compared with the control group 1. Group 4 and 5 showed a significant reduction in Catalase and superoxide dismutase activities at $P<0.05$, whereas, group 2, 3 and 6 was not statistically significant when compared to control group at $P>0.05$. A similar report by Haytham *et al.* (46) revealed a significant increase in MDA level, while antioxidant enzymes; GSH, superoxide dismutase and Catalase were significantly decreased after tramadol-treatment.

The pathological changes and oxidative damage induced by chronic use of tramadol can be explained by its capability to generate oxygen free

radicals that can attack and lead to destabilization and disintegration of the cell membrane as a result of lipid peroxidation (44). From our findings in table 4 and 5, after three-week withdrawal of chronic tramadol use, the same oxidative reduction changes were observed in group 6 as that in group 2. The oxidative reduction changes observed in group 6 animals could be as a result of depression, a well–documented withdrawal symptom of tramadol (42, 43), and the role of oxidative stress in the development of cognitive and memory impairment has be proved by several research studies (5, 6).

Toxic effect of tramadol administration can lead to a large population of unquenched free radicals leading to a state of oxidative stress (7). This is evidence in inhibition in the activities of antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT) in rat tissue as seen in this study. Superoxide dismutase and Catalase are important antioxidant enzymes which played a pivotal role in scavenging of oxidative free radicals (7).

Glutathione (GSH) has been known in preventing damage to important cellular components caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides, and heavy metals (8). While GSH protects cells by neutralizing or reducing reactive oxygen species (9, 10), Malondialdehyde (MDA) level indirectly reflect the extent of cellular damage by free radicals and are widely used as an index of free radical mediated lipid peroxidation (47).

In table 6 and 7, there was a decreased in reduced GSH and a significant increase in MDA level in rats treated with tramadol (30mg/kg) when compared to the control group. These results was similar with the recorded data of Elwy and Tab, (48) which reported that administration of tramadol for 30 days induced significant decrease in hepatic tissue SOD, CAT activities and GSH concentration as compared to control rats. Furthermore, Nafea *et al.* (49) demonstrated that abuse of tramadol for one month caused significant elevation in MDA (marker of lipid peroxidation) with reduction in the antioxidant (CAT) activity. Ahmed and Kurkar, (44) recorded a similar finding in testicular tissue as they reported that tramadol increases the testicular levels of nitric oxide (NO) and lipid peroxidation and significantly decreases the enzymatic antioxidant activities compared with the control group; as well as immune-histochemical examinations showed that tramadol increased the expression of endothelial nitric oxide synthase in testicular tissues. El-Gaafarawi (45, 46) also reported a significant increase in serum malondialdehyde levels in tramadol-treated rats indicating an increase in lipid peroxidation. Chronic tramadol use in research had been reported to significantly increase the level of adrenal MDA, in addition to a significant decrease in the level of antioxidant enzymes (GSH-Px and TR) in the blood (11). Ghoneim *et al.* (43) and Nna and Osim, (42) also studied the oxidative stress markers during and after withdrawal of tramadol administration. Their study revealed that chronic tramadol use increases the level of MDA and decreases the level of catalase, superoxide dismutase, and glutathione peroxidase in both testicular and brain tissues and improvement of these markers occurred after tramadol withdrawal. This was evident in the results of table(s) 4, 5, 6 and 7 of this study. These findings are of importance to be considered in patients who use tramadol as a pain killer, especially in the long term conditions.

5.0 Conclusion

Tramadol consumption lowers RBC count,

haemoglobin level, PCV, platelet count, WBC count, Catalase, SOD, and GSH activities while significantly raising MDA levels, resulting in hypoxic hypoxia, which can lead to severe and rapid apotosis, poor immunity, and the inability to pivot the role in scavenging oxidative free radicals and protecting cells by neutralizing or reducing reactive oxygen species. Hence, tramadol should only be used under medical supervision and only on prescription, avoiding indiscriminate and long-term use because therapeutic doses or severe doses might cause harm.

ETHICAL APPROVAL

The protocol of the experiments in this study was examined and approved by the Research, Ethics and Grants Committee of the Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria. This research was performed in accordance with the ethical standards on the care and use of animals as laid down (Helsinki, 1964).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Celik I and Suzek H. The hematological effects of methyl parathionin rats. *J. Haz. Mat 2008;* 153:1117-1121.
2. Oyedemi, S.O., Bradley, G. and Afolayan, A.J. *In-vitro* and *-vivo* antioxidant activities of aqueous extract of *Strychnos henningsii* Gilg. *Afr. J. Pharm. Pharmacol* 2010; 4: 70-78.
3. Soetan, K. O., Akinrinde, A. S., and Ajibade, T. O. Preliminary studies on the haematologicalparameters of cockerels fed raw and processed guinea corn (Sorghum bicolor): Proceedings of 38th Annual Conference of Nigerian Society for Animal Production 2013; 49-52
4. Abiodun Olusoji Owoade, Adewale Adetutu and Olubukola Sinbad Olorunnisola. Hematological and Biochemical Changes in Blood, Liver and Kidney Tissues under the Effect of Tramadol Treatment. *J Alcohol Drug Depend* 2019; 7:5
5. Schroeder, J. W.; Bauer, M. L.; Soto-Navarro, S. A. Wet corn gluten feed fed fresh or stored and supplemented with rumen undegradable protein in the diets of lactating dairy cows. *Professional Animal Scientist* 2005; 21 (4): 254-262
6. Hosseini-Sharifabad A, Rabbani M, Sharifzadeh M, Bagheri N. Acute and chronic tramadol administration impair spatial memory in rat. *Research in pharmaceutical sciences* 2016; 11:49
7. Kruidenier L, van Meeteren ME, Kuiper I. Attenuated mild colonic inflammation and improved survival from severe DSS-colitis of transgenic Cu/Zn-SOD mice. *Free Radic Biol Med* 2003; 34:753–765.
8. Pompella, A. Visvikis, A. Paolicchi, V.D. Tata, A.F. Casini. The changing faces of glutathione, a cellular protagonist Biochem. *Pharmacol* 2003; 66:1499-1503
9. Francesca Silvagno, Annamaria Vernone and Gian Piero Pescarmona. The Role of Glutathione in Protecting against the Severe Inflammatory Response Triggered by COVID-19. *Antioxidants* 2020; 9, (624): 1-16 Asima Bhattacharyya
10. , Ranajoy Chattopadhyay, Sankar Mitra, and Sheila E. Crowe. Oxidative Stress: An Essential Factor in the Pathogenesis of Gastrointestinal Mucosal Diseases. *Physiol Rev* 2014; 94(2): 329–354.
11. Mahmoud MF, Gamal S, Shaheen MA, El-Fayoumi HM. The effects of tramadol on hepatic ischemia/ reperfusion injury in rats. *Indian J Pharmacol* 2016; 48(3):275-280.

12. Ellman GL. Tissue sulfhydryl groups. Arch. Biochem. Biophys 1959; 82: 70-77
13. Beutler, E., Duron, O. and Kelly, B.M. Improved Method for the Determination of Blood Glutathione. Journal of Laboratory and Clinical Medicine 1963; 61, 882-888.

Vivian Ogwu

14. . A modified catalase assay suitable for a plate reader and for the analysis of brain cell cultures. Journal of Neuroscience Methods 1996; 670(1): 53-56.
15. Misra HP and Fridovich I. The role of superoxide ion in the antioxidation of epinephrine and a simple assay for superoxide dismutase. *J Biol Chem* 1972; 247:3170–3175.
16. and . Copper-dependent hydroxyl radical damage to ascorbic acid: formation of a thiobarbituric acid-reactive product. FEBS Lett. 1982; 25; 137(2):327-330.
17. Ossai N.R, Ojieh E.A, Nwogueze C.B, Olowe G.T and Ajayi E.R. Ameliorative potentials of methanolic stem bark extract of *nephrolepis undulate* in streptozotocin-induced diabetic wistar rats. *Plant Cell Biotechnology and Molecular Biology* 2021; 22(15&16):41-53
18. Baselt RC. Disposition of toxic drugs and chemicals in man. Seal Beach, California: *Biomedical Publications* 2011; 1712-1715
19. Grond S and Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004; 43(13): 879-923
20. Randall C and Crane J. "Tramadol deaths in Northern Ireland: a review of cases from 1996 to 2012". *Journal of Forensic and Legal Medicine. 2014; 23: 32–36.*
21. Fischer, Jnos and Ganellin, C. Robin. Analogue-based Drug Discovery. *John Wiley & Sons. 2006; p. 528.*
22. Singhal P C, Sharma P, Sanwal V, Prassad A, Kapasi A, Ranjan R, Franki N, Reddy K, and Gibbons N. Morphine modulates proliferation of kidney fibroblasts. *Kidney Int* 1998; **53**: 350–357.
23. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: a review of 114 cases. *Human and experimental toxicology* 2008; 27(3):201-205.
24. Raffa RB, Buschmann H, Christoph T, Eichenbaum G, Englberger W, Flores CM. Mechanistic and functional differentiation of tapentadol and tramadol. *Expert Opin Pharmacother* 2012; 13(10):1437-1449.
25. Ide S, Minami M, Ishihara K, Uhl G.R, Sora I, Ikeda K. Mu opioid receptor dependent and independent components in effects of tramadol, *Neuropharmacology* 2006; 51:651–658.
26. El-Gaafarawi I. Biochemical toxicity induced by tramadol administration in male rats. *Egyptian J Hospital Med* 2006; **23**:353 –362.
27. Mohammed, Hanaa and Mahmoud, Ayman. Chronic exposure to the opioid tramadol induces oxidative damage, inflammation and apoptosis, and alters cerebral monoamine neurotransmitters in rats. Biomedicine and Pharmacotherapy 2019; 110. 239-247. 10.
28. Brondani, J. T.; Luna, S. P.; Marcello, G. C. and Padovani, C. R. "Perioperative administration of vedaprofen, tramadol or their combination does not interfere with platelet aggregation, bleeding time and biochemical variables in cats". *Journal of Feline Medicine and Surgery* 2009; 11(6):503-509.
29. Işik, B., Arslan, M., Ozsoylar, O. and Akçabay, M. "Effects of preoperative lornoxicam versus tramadol on postoperative pain and adverse effects in adult tonsillectomy patients". *Agri* 2009; 21(3):113-120.
30. Hanem Mohammed Roshdy, Rania Hamed Abdel-Rahman, Hanan Azzam and Amal Abd El-Salam El-Bakary. Repeated Tramadol Administration Induced Bleeding in Albino Rats. *Mansoura J. Forens. Med. Clin. Toxicol* 2018; 26(2): 169 – 177.

31. Nna VU, Victor O, Oka AL, Udefa EO, Ofutet OE and Ofem. High Doses of PDE5 inhibitors and tramadol reversibly alters haematological parameters in rats. *Journal of Applied Pharmaceutical Science* 2016; 6(04): 086-092.
32. Aldalou, AR, Abdel-Aziz I. and Shahwan O. Impact of giving sildenafil (viagra) / tramadol (tramal) combination on the blood of domestic rabbits. *Journal of Science* 2014; 4(3): 162-169.
33. Udegbunam RI, Okereke HN. and Udegbunam SO. Single versus repeated tramadol injectionin laparotomized albino rats: comparison of effects on hematology, serum biochemical parameters, and bodyweight gain. *Journal of Advanced Veterinary and Animal Research* 2015; 2(3): 316-320.
34. Goeringer, K.E; Barry K.; logan, and Gary D. Christian. Identification of Tramadol and its metabolite in blood from drug related death and drug impaired-drivers. *Journal of Analytical Toxicology* 1997; 21:529-537.
35. Mohammed A. Aldiwan; Adel M. Hassan Alzobidy; Mohammed A. Younis. The effect of Tramadol on some blood and biochemical parameters of male rats (Rattus norvegicus). *Baghdad Science Journal* 2015; 12(3) *496 -502.*
36. Abiodun Olusoji Owoade, Adewale Adetutu and Olubukola Sinbad Olorunnisola. Hematological and Biochemical Changes in Blood, Liver and Kidney Tissues under the Effect of Tramadol Treatment. *J Alcohol Drug Depend* 2019; 7(5): 1 -7
37. Gipson DC and Kalivas WP. Neural Basis of Drug Addiction. In: De Micheli D, Andrade MAL, da Silva AE, de Souza Formigoni OML, eds. Drug Abuse in Adolescence: Neurobiological, Cognitive, and Psychological Issues. Switzerland: Cham: Springer International Publishing 2016; 37–56.
38. Cadet JL, Bisagno V, Milroy CM. Neuropathology of substance use disorders. *Acta Neuropathol* 2014; 127(1):91–107.
39. Cunha–Oliveira T, Rego AC, Oliveira CR. Cellular and molecular mechanisms involved in the *Nafea OE et al. Int J Sci Rep* 2016; *2(7):143-154.*
40. Elyazji, N. R., I. Abdel-Aziz, A. Aldalou, and O. Shahwan. The effects of tramadol hydrochloride administration on the hematological and biochemical profiles of domestic male rabbits. IUG *J Natural and Eng Studies* 2013; 21: 51-65.
41. Akhtardanesh, B., Sharifi, H., Rasodi, R. and Aghazamani, M. Evaluation of haematological and biochemical changes after short term tramadol usage in healthy dogs. *Iranian Journal of Veterinary Medicine* 2014; 8(1): 41-45.
42. Nna VU and Osim EE. Testicular toxicity following separate and combined administration of PDE5 inhibitors and opioid: Assessment of recovery following their withdrawal 2016; *Andrologia;*
43. Ghoneim, F.M., Khalaf, H.A., Elsamanoudy, A.Z and Helaly, A.N. "Effect of chronic usage of tramadol on motor cerebral cortex and testicular tissues of adult male albino rats and the effect of its withdrawal: histological, immunohistochemical and biochemical study," *International Journal of Clinical and Experimental Pathology* 2014; 7(11); 7323–7341.
44. Ahmed MA and Kurkar A. Effects of opioid (tramadol) treatment on testicular functions in adult male rats: The role of nitric oxide and oxidative stress. Clin Exp Pharmacol Physiol 2014; 41:317–23
45. El-Gaafarawi I.I. Biochemical toxicity induced by tramadol administration in male rats. Egypt J Hosp Med 2006; 23:353–362 Haytham A. Ali
46. , Mohamed Afifi, Taghred M. Saber, Arwa A

Makki, A.T. Keshta, Mohammed Baeshen and Ammar AL-Farga. Neurotoxic, Hepatotoxic and Nephrotoxic Effects of Tramadol Administration in Rats. *J Mol Neurosci*. 2020 https://doi.org/10.1007

47. Mansour, MA. Protective effects of thymoquinone and desferrioxamine against hepatotoxicity of carbon tetrachloride in mice. *Life Sci* 2000; 66(26): 2583-2591
48. Elwy, A.M. and Tab, G. Effects of Chronic Usage of Tramadol, Acetaminophen and Tramaceton Some Biochemical and Immunological Changes in Male Rats. *J Drug Res Egypt* 2014; 35*(1), 63-71.*
49. Nafea, OE., ElKhishin, IA., Awad, OA., Mohamed, DA. A study of the neurotoxic effects of tramadol and cannabis in adolescent male albino rats. *Int J. Sci Rep* 2016; 2(7): 143-154.
50. Dubner R. A bibliometric analysis of the pain Journal as a representation of progress and trends in the field. *Pain* 2009; **142** (1–2):9–10.
51. World Medical Association. "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects". JAMA 2013; 310 (20): 2191–2194

Citation: This article should be cited as: Ojieh AE, Ossai NR, Nwogueze BC. Assessment of Haematological And Antioxidants Changes In Male Albino Wistar Rats Treated With Tramadol. Afr. J. Trop. Med. & Biomed. Res. 2022; 5(2): 30-42