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ORIGINAL ARTICLE

Association of Pre-Hospital Steroid and Antibiotic Use with Hematological Severity and Liver Injury in Dengue Patients in Karachi Outbreak: A Cross-Sectional Study

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ABSTRACT

Background: Inappropriate pre-hospital steroid and antibiotic use is common in dengue outbreaks in Karachi but little is known about how these treatments affect liver damage and hematological severity. The purpose of this study was to evaluate the relationship between pre-hospital exposure to steroids and antibiotics and laboratory-based severity markers in dengue patients during a recent outbreak.

Methodology: Over the course of four months a cross-sectional questionnaire-based study involving 130 dengue-positive patients was carried out at a tertiary care hospital in Karachi. Demographics pre-hospital steroid and antibiotic use and clinical course were recorded using a structured questionnaire given by the interviewer. Chi-square tests t-tests and multivariable regression were used to adjust for age sex comorbidities and dengue severity. Hematological severity (platelet count hemoconcentration) and liver injury markers (ALT AST bilirubin albumin) were taken from hospital records.

Results: Antibiotic use was reported in 44. 6% of patients and steroid use in 31.5% of patients prior to hospitalization. The median platelet count was lower in steroid-exposed patients (42.0 vs. 68.5 × 10⁹/L; $p < 0.001$) higher rates of severe thrombocytopenia (68.3% vs. 23.6%; $p < 0.001$) and more hemoconcentration (53.7% vs. 26.9%; $p = 0.004$). They also showed higher ALT ((124.0 vs. 82.0 U/L; $p < 0.001$) and AST with 34. 1 percent exhibiting severe transaminitis (ALT >5× ULN) as opposed to 5.6% for non-users. Pre-hospital steroid use was verified by multivariable analysis as an independent predictor of elevated transaminases and severe thrombocytopenia ($p < 0.001$). Use of antibiotics by itself did not exhibit any meaningful independent correlations. Patients exposed to steroids experienced longer hospital stays more ICU admissions and a non-significant trend toward increased mortality.

Conclusion. In Karachi dengue patients' pre-hospital steroid use is significantly linked to increased hematological severity and liver damage while antibiotics by themselves did not demonstrate similar independent effects. During dengue outbreaks routine community-level steroid prescriptions should be discouraged. To improve guideline-adherent management specific educational interventions for primary care and pharmacy-level providers are required.

Keywords: Pre-Hospital Steroid, Antibiotic, Hematological Severity, Liver Injury, Dengue, Karachi

INTRODUCTION

Over the past ten years dengue fever has become one of the most significant arboviral infections in the world with frequent and occasionally explosive outbreaks occurring in Pakistan especially in Karachi. The illness is caused by four serotypes of the dengue virus (DENV-1–4) which are spread by Aedes mosquitoes[1]. Clinical symptoms range from a mild fever to potentially fatal dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Many patients have shown signs of thrombocytopenia leukopenia elevated hematocrit and transaminitis during recent outbreaks in Karachi[2]. These conditions are strongly linked to increased disease severity and a higher risk of complications like massive bleeding acute liver damage and shock-related organ failure[3]. A significant percentage of hospitalized dengue cases have been reported to have liver-related abnormalities such as elevated bilirubin aspartate aminotransferase (AST) and alanine aminotransferase (ALT) highlighting the liver as a crucial target organ and a predictor of unfavorable outcomes[3,4]. Dengue has changed from occasional cases to seasonal epidemics in Karachi which are frequently attributed to unplanned urbanization climate variability and insufficient vector-control measures. Between 2019 and 2023 cross-sectional and hospital-based studies revealed an increasing prevalence of laboratory-confirmed dengue with severe cases frequently clustering among adults and young adults who visit emergency rooms. Severe dengue patients have significantly lower platelet counts more severe leukopenia and higher liver-enzyme levels than non-severe cases according to data from Pakistan. Complications like significant thrombocytopenia fluid accumulation and acute hepatitis are becoming more widely acknowledged[5,6].

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Studies have shown a strong correlation between elevated liver enzymes and severity scores longer hospital stays and worse outcomes in cases of dengue liver injury which can range from mild transaminitis to fulminant hepatic failure[3,7]. These results emphasize the necessity of identifying high-risk patients early and closely monitoring hepatic and hematological parameters during acute infection[4,6]. Many patients in Karachi seek treatment from primary care physicians' community clinics or non-allopathic practitioners prior to being admitted to the hospital. In these settings empirical treatments like corticosteroids and antibiotics are commonly given for atypical presentations persistent fever or suspected sepsis[1,4]. Despite the fact that steroids are occasionally used to try to reduce inflammation or thrombocytopenia in moderate-to-severe dengue randomized and observational data are still inconclusive. According to some reports corticosteroid use may mask the natural course of platelet recovery or prolong illness duration without clearly reducing mortality[8]. Despite guidelines emphasizing that antibiotics have no role in uncomplicated dengue and may contribute to drug-related hepatotoxicity or needless microbial resistance doctors may prescribe broad-spectrum antibiotics in resource-limited settings when bacterial co-infection is suspected or when dengue is initially misdiagnosed[2,8]. Pre-hospital exposure to hepatotoxic drugs especially long-term or high-dose steroids and some antibiotics may exacerbate hepatic dysfunction and mask the actual effects of viral damage on the liver because dengue-associated liver injury can already result in significant elevation of transaminases and bilirubin. 318. In light of this despite frequent outbreaks and a high case load the relationship between pre-hospital steroid and antibiotic use and the development of severe hematological disturbance or acute liver injury in dengue patients is still poorly characterized in cohorts based in Karachi[1,5-6].

Previous research from Pakistan has either concentrated on liver-function correlates clinical predictors of severity or limited assessments of corticosteroids in in-hospital settings however few have thoroughly investigated the effects of early drug exposure at the community level on hematological and hepatic outcomes[9,10]. The current study uses a cross-sectional design to examine the relationship between pre-hospital use of steroids and antibiotics and the degree of hematological severity (particularly thrombocytopenia leukopenia and hemoconcentration) and liver-injury markers (ALT AST bilirubin albumin) in dengue patients during a recent outbreak in Karachi. In order to provide evidence-based recommendations for community-level prescribing practices and referral pathways in upcoming dengue seasons the main goal is to ascertain whether such pre-admission therapies independently affect markers of disease severity and hepatic dysfunction.

METHODOLOGY

During a recent four-month dengue outbreak a cross-sectional questionnaire-based study was carried out at a tertiary care hospital in Karachi Pakistan (March–June 2023). Participants were all consecutive patients admitted with laboratory-confirmed dengue infection as indicated by positive dengue NS1 antigen and/or IgM-IgG serology. Patients who refused to give their consent had incomplete medical records or were younger than one year old were not included. Dengue-positive inpatients who visited the study hospital during the four-month outbreak window made up the target population. Convenience sampling was employed and patient recruitment continued until the predetermined sample size of 130 was reached. Based on previous cross-sectional dengue studies conducted in Pakistani tertiary centers which employed comparable sample sizes for sufficient power to identify correlations between treatment patterns and laboratory-based severity markers this n-value was chosen.

A structured interviewer-administered questionnaire created especially for this study was used to collect data. Three modules made up the instrument. clinical and demographic profile. weight sex age and comorbidities (e.g., immunosuppression diabetes mellitus hypertension and chronic liver disease). The primary presenting complaints (fever headache myalgia rash vomiting bleeding etc.) the duration of the fever prior to admission and the date the symptoms first appeared. etc. Details of the hospital admission: the date of admission the length of stay in the ward or intensive care unit and the final dengue severity category (severe dengue with warning signs or dengue fever) as determined by WHO 2009 guidelines. 40 and 41. Medication history prior to admission (steroids and antibiotics). Prior care provider (private clinic general practitioner pharmacy/chemist non-allopathic practitioner emergency room etc.). The following medications were taken prior to hospital presentation. Type (e) any steroid (yes/no), prednisolone dexamethasone) dosage method and time frame. Any prescribed medication (generic names) route duration indication (e) and antibiotic (yes/no). (g). sore throat persistent fever. When to start using steroids or antibiotics in relation to the onset of symptoms (within 24 48 72 or more than 72 hours). Using steroids or antibiotics over-the-counter or self-medicating. markers of severity based in the lab. parameters related to hematology at admission. hemoglobin hematocrit platelet counts total leukocyte count and hemoconcentration.

Markers of liver damage upon admission. Total bilirubin albumin alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Laboratory reports and the hospital information system are used to record daily laboratory values during hospital stays (admission day and day three). In addition to local outbreak data from tertiary centers in Karachi published literature on dengue severity liver-function correlations and corticosteroid use in dengue was used to operationalize questionnaire items. To ensure linguistic equivalency the instrument was prepared in English and when necessary, translated into Urdu using a back-translation technique. Under the principal investigators supervision skilled resident physicians and research assistants collected data. After a brief explanation of the study parents or guardians of pediatric patients or adult patients provided written informed consent. Within 24 hours of admission face-to-face interviews were used to complete the interviewer-administered questionnaire. To confirm medication history and severity markers medical records and laboratory reports were reviewed. A standardized data-entry form was used to enter all of the information into a secure electronic database. Pre-hospital steroid use associations (none vs. the use of antibiotics (none vs. Chi-square/Fishers exact tests independent-samples t-tests or Mann-Whitney U tests were used to assess any) with hematological severity and liver injury markers. Age sex comorbidities and dengue severity were taken into account using multivariable logistic regression models for severe thrombocytopenia and severe transaminitis and multivariable linear regression models for continuous ALT/AST. Statistical significance was defined as a two-sided p-value <0.05.

RESULTS

Over a period of four months 130 dengue-positive patients were enrolled. There were 52 (40.0%) female participants and 78 (60.0%) male participants with an average age of 32.4 ± 12.6 years. Adults (≥18 years 112 86.2%) made up the majority whereas children (1–17 years) made up 18 (13. 8%). Obesity (18, 13.8%) diabetes mellitus (21, 16.2%) and hypertension (29 22.3%) were common comorbidities. Prior to admission the median fever duration was 4.0 (IQR 3. 0–5. 0) days. Dengue severity was categorized as severe dengue (SD) in 27 cases (20. 8%) dengue fever (DF) in 49 cases (37. 7%) and dengue with warning signs (DWS) in 54 cases (41. 5%).

Antibiotic use was reported in 58 patients (44.6%) and steroid use in 41 patients (31.5%) prior to hospitalization. Prednisolone (23, 56.1%) and dexamethasone (14, 34.1%) were the most frequently administered oral formulations among the 36 (87.8%) steroid users. Steroid therapy was administered for a median of 3.0 (IQR 2. 0–4. 0) days prior to admission and 31 (75.6%) patients began taking steroids within 48 hours of the onset of symptoms. When a fever persisted or a bacterial infection was suspected antibiotics were typically prescribed. The most commonly used drugs were ceftriaxone (10, 17.2%) azithromycin (18, 31.0%) and amoxicillin-clavulanate (26 44.8%). Antibiotic use lasted 3.5 days on average (IQR 2. 0–5. 0 days). Antibiotics and steroids were administered to 18 (13. 8%) patients prior to hospitalization. Patients s had significantly lower platelet counts who received pre-hospital steroid and more severe hematological derangements (Table 3). Pre-hospital steroid exposure was strongly associated with higher liver-enzyme levels and more frequent severe transaminitis (Table 4). Antibiotic use alone did not show a comparable effect.

Table 1: Demographic and clinical characteristics of dengue patients (n = 130)

Variable	Category	n	%
Age group	1–17 years	18	13.8
	18–60 years	105	80.8
	>60 years	7	5.4
Sex	Male	78	60.0
	Female	52	40.0
Comorbidity	Hypertension	29	22.3
	Diabetes mellitus	21	16.2
	Obesity	18	13.8
	None	62	47.7
Dengue severity	Dengue fever (DF)	49	37.7
	Dengue with warning signs	54	41.5
	Severe dengue (SD)	27	20.8
Bleeding manifestations	Present	33	25.4
ICU admission	Yes	41	31.5

Table 2: Pre-hospital steroid and antibiotic use (n = 130)

Variable	Category	n	%
Pre-hospital steroid use	No	89	68.5
	Yes	41	31.5
Pre-hospital antibiotic use	No	72	55.4
	Yes	58	44.6
Both steroid and antibiotic use	No	112	86.2
	Yes	18	13.8
Route of steroids (among users)	Oral	36	87.8
	Parenteral (IV/IM)	5	12.2
Common steroid agents (n = 41)	Prednisolone	23	56.1
	Dexamethasone	14	34.1
Typical antibiotic agents (n = 58)	Amoxicillin-clavulanate	26	44.8
	Azithromycin	18	31.0
	Ceftriaxone	10	17.2

Table 3: Hematological severity by pre-hospital steroid and antibiotic use

Outcome / Category	No steroid (n = 89)	Steroid (n = 41)	p-value	No antibiotic (n = 72)	Antibiotic (n = 58)	p-value
Platelet count (×10⁹/L), median (IQR)	68.5 (52.0–90.0)	42.0 (28.0–55.0)	<0.001	62.0 (48.0–85.0)	54.0 (36.0–78.0)	0.12
Severe thrombocytopenia (<50 ×10⁹/L), n (%)	21 (23.6%)	28 (68.3%)	<0.001	30 (41.7%)	19 (32.8%)	0.27
Hemoconcentration (HCT rise ≥20%), n (%)	24 (26.9%)	22 (53.7%)	0.004	28 (38.9%)	18 (31.0%)	0.34
Multivariable adj. OR for severe thrombocytopenia (95% CI)	1.00 (ref)	4.21 (2.07–8.56)	<0.001	1.00 (ref)	1.18 (0.61–2.28)	0.62

Table 4: Liver-injury markers by pre-hospital steroid and antibiotic use

Outcome / Category	No steroid (n = 89)	Steroid (n = 41)	p-value	No antibiotic (n = 72)	Antibiotic (n = 58)	p-value
ALT (U/L), median (IQR)	82.0 (54.0–120.0)	124.0 (80.0–180.0)	<0.001	88.0 (58.0–130.0)	96.0 (62.0–145.0)	0.21
AST (U/L), median (IQR)	72.0 (48.0–110.0)	108.0 (70.0–150.0)	<0.001	76.0 (50.0–115.0)	84.0 (56.0–130.0)	0.19
ALT >5× ULN, n (%)	5 (5.6%)	14 (34.1%)	<0.001	7 (9.7%)	12 (20.7%)	0.07
Bilirubin >1.5 mg/dL, n (%)	20 (22.5%)	11 (26.8%)	0.59	17 (23.6%)	14 (24.1%)	0.95
Albumin (g/dL), mean ± SD	3.7 ± 0.5	3.4 ± 0.6	0.03	3.6 ± 0.5	3.5 ± 0.5	0.18
Multivariable β for ALT (95% CI)	—	28.4 (14.7–42.1)	<0.001	—	8.1 (–2.5 to 18.7)	0.13
Multivariable β for AST (95% CI)	—	24.1 (11.3–36.9)	<0.001	—	6.9 (–3.1 to 16.9)	0.17

DISCUSSION

Our cross-sectional study of 130 dengue patients during a 4-month outbreak at a tertiary care hospital in Karachi shows that pre-hospital corticosteroid use is strongly linked to more severe liver damage and hematological severity whereas antibiotics by themselves did not clearly have an independent impact on these outcomes. This is consistent with the larger body of research on hematological and hepatic abnormalities associated with dengue but it differs from some smaller studies that have suggested that early steroid therapy has neutral or even positive effects[11]. We found that patients who were given steroids prior to being admitted to the hospital had more frequent hemoconcentration higher rates of severe thrombocytopenia and significantly lower platelet counts[12]. These results support the role of thrombocytopenia as a crucial indicator of an unfavorable dengue prognosis and are consistent with a number of hospital-based studies from Pakistan that have found an inverse relationship between platelet count and disease severity. On the other hand short-course oral prednisolone did not significantly affect platelet counts shock or other major hematological endpoints in a randomized trial from Vietnam however the study lacked the power to identify slight variations in severity markers[13]. 49 The discrepancy between our observational data and this trial may be due to timing and context differences: the Vietnamese trial employed a controlled early-stage regimen that may mitigate adverse hematological effects while our Karachi cohort received steroids primarily in the community setting frequently without standardized protocols[14,15].

In a low- and middle-class setting where platelet-count monitoring is not always easily accessible the independent correlation between steroid use and severe thrombocytopenia in our multivariable model is especially worrisome. Similar findings from other research have demonstrated that hemoconcentration and platelet count are reliable indicators of the development of severe dengue and shock-related complications[16]. As a result, our results corroborate the World Health Organizations (WHO) current recommendations that steroid therapy should only be used in controlled research settings and is not advised for the routine treatment of dengue. According to our findings pre-hospital steroid exposure was linked to increased ALT and AST admission levels a higher percentage of severe transaminitis and slightly lower albumin levels all of which are indicative of increased liver damage[17]. This is consistent with hospital-based cohorts from South Asia and Karachi that found elevated transaminases in 70–80% of dengue patients and showed a direct link between enzyme elevation and the severity of the illness. Even in cases of mild viral hepatitis the use of hepatotoxic or immuno-modulating drugs during dengue infection can worsen liver damage according to a number of narrative and cohort studies[16,18]. Although the role of antibiotics alone was not statistically significant in our sample our discovery that patients receiving both steroids and antibiotics had the highest transaminase levels suggests an additive or synergistic effect[19].

Corticosteroids may be safe in early-stage dengue according to some small trials and case series that have found no appreciable liver-enzyme deterioration with short-course steroid use. The baseline severity of liver involvement as well as the dose duration and timing of steroid administration may contribute to this disparity[20]. Steroids are frequently administered in larger doses for longer periods of time and without sufficient laboratory monitoring in community-based prescribing (as in the case of our Karachi patients) which may reveal subclinical hepatotoxicity [17]. Our cohort frequently used pre-hospital antibiotics which is indicative of the propensity to misdiagnose dengue as a bacterial infection or coinfection particularly during febrile outbreaks. After adjustment antibiotics were not independently linked to thrombocytopenia or severe liver damage which is generally in line with the belief that antibiotics are only useful in treating confirmed bacterial superinfection in cases of uncomplicated dengue. The promotion of antimicrobial resistance and possible drug-related hepatotoxicity are two indirect risks associated with excessive empirical antibiotic prescriptions especially when combined with other medications like corticosteroids. These factors highlight the significance of enhanced clinician education and diagnostic capability in primary care and community-level settings[21,22].

Although our sample size was small for survival analysis patients who received pre-hospital steroids had longer hospital stays higher ICU admission rates and a non-significant trend toward higher mortality[23]. This is consistent with findings from cohorts in Karachi that have associated longer hospital stays and higher mortality rates with severe hepatitis (ALT 300 IU/L). Similar findings from other research have demonstrated that hypoalbuminemia and severe liver damage are independent predictors of poorer outcomes in dengue-related shock and critical illness[22,24]. These convergent data imply that steroid exposure at the community level may result in worse clinical outcomes and more resource-intensive in-hospital care in addition to amplifying laboratory-based markers of severity[25]. Our research contributes to the increasing amount of evidence that dengue-management

algorithms should specifically discourage routine pre-hospital corticosteroid use and place an emphasis on early warning sign recognition timely fluid management and cautious use of unnecessary or hepatotoxic medications. Future research should examine whether structured educational interventions for Karachis community pharmacists and primary care physicians can lower the number of inappropriate prescriptions for antibiotics and steroids during dengue seasons[26,27].

CONCLUSION

Among dengue patients in Karachi pre-hospital steroid use was substantially linked to lower platelet counts increased rates of severe thrombocytopenia and hemoconcentration elevated ALT and AST levels and longer hospital stays. Hematological severity and liver damage were not clearly affected by antibiotic use alone. These results support the strict restriction of corticosteroids in routine dengue management and show that community-level steroid exposure amplifies laboratory-based markers of dengue severity and liver damage without any discernible benefit.

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