Clinical aspects of dengue fever in children attended Mukalla city hospital-Yemen

الجوانب السريرية للأطفال المصابين بحمى الضنك المترددين على مستشفى مدينة المكلا - اليمن

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Abstract :

Dengue fever is a mosquito-borne disease that is spread rapidly in new governorates in Yemen in the last ten years.

Objectives: The aim of this study was to assess the clinical profiles of children involvement by dengue virus attended Mukalla city hospital, Mukalla,Yamen from January 2015 to December 2015.

Study Design: This cross-section study consisted of 100 children with age range from 6months -14 years (mean age +/- SD, 9.76 ± 3.64 years) who serologically confirmed to have dengue fever and attended Mukalla city hospital. A detailed symptomatology, clinical findings, and investigations were recorded. The patients were divided into three groups according to revised World Health Organization 2009 criteria,dengue fever without warning signs (Group D), dengue fever with warning signs (Group DW) and severe dengue (Group SD).

Results: Out of 100 dengue cases, 60% patients were male and 40% were females (P < 0.05). The majority of the dengue cases were found in the age group of 11-14(46%). The percentage of dengue cases was significantly higher in urban compared to rural (56% versus 44%,P<0.05). The highest percentage of cases were found to be DW (60%), followed by D 25% and SD (15%). All patients suffered from fever (100%). Persistent vomiting was present in 22(36.7%) of group DW and 10 (66.7%) of group SD (P < 0.05). Abdominal pain was significant higher in group DW (n=45, 75 %) and group SD (n= 13, 86.7 %) compared to group D (n=3, 12 %) (P < 0.05). Jaundice was observed in 1 (1.7%) of Group DW and 3 (20 %) of Group SD (P < 0.05).Hepatomegaly was observed in 18 (30%) of Group DW and 9 (60 %) of Group SD (P < 0.05). Ascites and pleural effusion were significant higher in group SD (n =4, 26.7 % and n =5, 33.3%,respectively) compared to group DW (n=3, 5% and 4, 6.7 %,respectively)(P< 0.05).

The mean platelet count level of the patients were 95.80±77.79, 57.66±47.06,41.62±21.69, in groups D,DW and SD, respectively (P<0.05). For patient with groups D,DW, and SD, mean Aspartate Transaminase (AST) values were, 55.50±14.40, 80.00±15.80 and 130.00±15.80 respectively (P<0.05) and mean Alanine Transaminase (ALT) values were, 47.90±10.30, 76.10±11.60,and 110.00±11.80 respectively (P < 0.05). Out of the 100 specimens, 20% were positive for primary infection (IgM) and 80% were positive for secondary infection (IgM and IgG).

Conclusions: Male sex and children 11– 14 years were most affected by dengue fever with the majority of cases from urban areas. Persistent vomiting, abdominal pain, jaundice, hepatomegaly, ascites, pleural effusion and hepatomegaly were found significantly high in severe dengue cases which can be used as possible markers of severe dengue.

Keywords: Child, Dengue, Revised classification, Warning signs, World Health organization.

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الملخص بالعربي :

المقدمة: حمى الضنك هي مرض انتشر سريعاً في محافظات جديدة في اليمن في السنوات العشر الأخيرة.

هدف الدراسة: هذه الدراسة قيمت الملامح السريرية للأطفال المصابين بحمى الضنك المترددين على مستشفى مدينة المكلا في الفترة ما بين يناير ٢٠١٥م، وديسمبر٢٠١٥م.

طريقة الدراسة: أجريت هذه الدراسة المقطعية على ١٠٠ حالة مصابة بحمى الضنك، وتم تأكيد التشخيص بواسطة مقايسة الممتز المناعي المرتبط بالأنزيم المتوفر تجارياً، وقد تراوح أعمار الأطفال المرضى من ٦ أشهر إلى ١٤ سنة ومتوسط العمر ٩ سنوات، وقد تم إملاء استبيان معياري معد لهذا الغرض، وتم تقسيم المرضى وفقا لمعيار سنة ٢٠٠٩ لمنظمة الصحة العالمية إلى ثلاث مجاميع، كالآتي : المجموعة (أ) حمى الضنك دون سابق إنذار، والمجموعة (ب) حمى ضنك بسابق إنذار، والمجموعة (س) حمى ضنك شديدة. وقد تم جمع بيانات نتائج الفحص السريري وتحاليل الدم والتحاليل الكيميائية الخاصة بكل حالة، وتم تحليلها إحصائيا باستخدام برنامج الحزمة الإحصائية للعلوم الاجتماعية.

النتائج: لوحظ بأن من ١٠٠ حالة من الأطفال المصابين بحمى الضنك، ٦٠ حالة هم من الذكور و٤٠ حالة إناث، وأكثر الحالات إصابة كان عمرها من ١١ -١٤سنة، وأكثر الحالات كانت من المدن. ووفقا لتقسيم الحالات فإن المجموعة (ب) هي الأكثر شيوعاً بنسبة (٦٠٪)، ثم المجموعة (أ) بنسبة (٢٥ ٪) وأخيرا المجموعة (س) بنسبة (١٥٪). كل المرضى كانوا يعانون من ارتفاع في درجة الحرارة، وقد كان القيء الدائم وآلام البطن أكثر ظهوراً في المجموعة (ب) والمجموعة (س)، مقارنة بالمجوعة (أ).

ولوحظ أن اليرقان وتضخم الكبد أكثر ظهوراً في حالات المجموعة (س) مقارنة بالمجموعتين(أ) و(ب)، وإن الاستسقاء والانصباب الجنبي أكثر ظهوراً في المجموعة (س) مقارنة بالمجموعة (ب)، ولا يوجد في المجموعة (أ). وكذلك لوحظ إن السبات العميق والأرق كان أكثر ظهوراً في المجموعة (ب) والمجموعة (س) مقارنة بالمجموعة (أ).

إن مستوى انخفاض عدد الصفائح الدموية في حالات المجموعتين (ب) و(س) اكثر مقارنة بالمجموعة (أ) و أن نسبة الصفائح الدموية ما بين (٤١٠٠٠ -٥٠٠٠٠) في حالات المجموعتين (ب) و(س) أكثر ظهوراً مقارنة بالمجموعة (أ) .

وقد وجدت هذه الدراسة أن إنزيمات الكبد أكثر ارتفاعاً في المجموعتين (ب) و(س) مقارنة بالمجموعة (أ) وأن العدوى الثانوية أكثر شيوعاً من العدوى الأولية.

الخلاصة: أكثر الأطفال إصابة بحمى الضنك تتراوح أعمارهم من ١١ -١٤ ومعظمهم في المناطق الحضرية.

حمى الضنك تشمل مجموعة من العلامات والأعراض، ولها فحوصات مخبرية. ومن المهم أن يكون هنالك مؤشرات عالية لتحديد حمى الضنك في المناطق الموبوءة.

الكلمات المفتاحية: الأطفال - حمى الضنك - تصنيف منقح - علامات الحذر - منظمة الصحة العالمية.

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INTRODUCTION :

Dengue disease is an acute infectious disease caused by four serotypes of dengue virus and is the most prevalent mosquito-borne viral disease in humans, occurring in tropical and subtropical countries of the world where over 2.5 billion people are at risk of infection (1).

Historically, dengue has been reported in Yemen as early as the 19th century, and more frequent outbreaks of dengue have emerged since 2000, but some of these outbreaks were not well-documented or published, which was the case in Shabwah governorate in 2001, 2002, and 2005 and the outbreaks in Aden and Taiz (2010), Hadramout-Mukalla (2005), and Al-Hudidah governorate (1994, 2000, 2004, and 2005) (2). There are certain salient clinical features, which help in the detection of dengue fever cases, but they can also present with varied clinical manifestations (3). The clinical classification was revised as dengue without warning signs, dengue with warning signs, and severe dengue (WHO, 2009). It helped in identifying sick dengue patients easier for the clinicians than the traditional guidelines (4).

The warning signs in the revised classification were put forth to identify the severe dengue cases by health care professionals early during endemic and facilitated them for the need of admission and more intensive monitoring without the help of detailed laboratory workup (5).

This study aimed to assess the clinical profile of children involvement by dengue virus attended Mukalla city hospital.

METHODS :

A cross section study of 100 children in the age group of 6 months -14 years with a mean age of 9.76 ± 3.64 years who were serologically confirmed to have dengue attended Mukalla city hospital between January 2015 and December 2015 were included in the study. Informed consent from relatives of patients was taken.

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The patients were divided into three groups according to revised World Health Organization 2009 criteria,dengue fever without warning signs (Group D), dengue fever with warning signs (Group DW) and severe dengue (Group SD).

WHO 2009 guideline, probable dengue (Dengue without warning signs) was defined as live in/travel to dengue endemic area with fever and two of the following: nausea, vomiting; rash; aches and pains; tourniquet test positive; leucopenia; any warning sign. Dengue with warning signs: Dengue, as defined above with any of the following Warning warning signs, were abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy and restlessness, liver enlargement >2 cm. Laboratory: increase in HCT with a concurrent rapid decrease in platelet. Criteria for severe dengue was severe plasma leakage leading to dengue shock syndrome, fluid accumulation with respiratory distress; severe bleeding; severe organ involvement (liver: AST or ALT >1000, impaired consciousness and multiple-organ dysfunction syndrome was considered when dysfunction involved ≥2 organs. (WHO, 2009)(2).

Inclusion criteria were children with fever of 2-7 days who fits into the clinical case.

Excluded from the study, patients with weight less than 8kg, age less than 6 months, children with any specific identified bacterial or viral febrile illness of more than two weeks.

The patient demographic variables, presenting complaints and examination findings were recorded on a structured questionnaire.

For all children, the following investigations were done, complete blood count, platelet count,serum urea and creatinine, liver enzymes (AST and ALT), Chest x-ray and abdominal ultrasound.

The blood samples were taken from suspected cases after 4-6 days from onset of fever. The serum was separated, collected and stored in a sterile container and kept at 2 - 8°C for a maximum of 7 days until they were transported to the laboratory where they were

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tested for the presence of dengue IgM and IgG antibodies employing capture enzyme linked immunosorbent assays (ELISA)Kits according to manufacturer protocal.

Statistical methods:The data were processed and analyzed by Statistical Package for Social Sciences (SPSS) software (version 17). For determination of quantitative data, mean and standard deviation were used. The Mann-Whitney U and Kruskal-Wallis tests were used to determine statistical significance for continuous variables, and chisquare test for categorical variables. Multivariate logistic regression analyses were performed to identify the association between clinical profiles and severe dengue virus infection in children. P< 0.05 was considered significant.

RESULTS :

Table (1): Demographic data of studied groups:

It was observed that out of 100 dengue cases, 60% patients were male and 40% were females (P < 0.05).The majority of the dengue cases were observed in the age group of 11-14 with 46% followed by the age group of 6-10 years with 34%, then at the age group of 1-5 years with 19% and at the age group of <1 year with 1%. It was also found that percentage of cases with dengue was significantly higher in urban 56% compared to rural 44 %. (P < 0.05).

Figure (1): Percentage of dengue cases severity:

The highest percentage of cases were found to be DW(60%), followed by D (25%) and SD (15%).

Table (2):Clinical characteristic of the studied groups:

All patients suffered from fever (100%). Persistent vomiting was present in 22(36.7%) of group DW and 10 (66.7 %) of group SD (P<0.05). Abdominal pain was significant higher in group DW 45 (75%) and group SD 13 (86.7%) compared to group D 3(12%) (P<0.05).The jaundice was observed more in group SD 3(20%) compared to group DW 1(1.7%)(P < 0.05). Hepatomegaly was present

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in 18 (30%) of Group DW and 9 (60%) of Group SD (P < 0.05). Ascites and pleural effusion were significant higher in group SD 4(26.7%) and 5(33.3%), respectively compared to group DW 3 (5%) and 4(6.7%)respectively (P<0.05).Shock was present only in SD (n=2, 13.3%). Impaired consciousness was present only in SD (n=3, 20 %).

Table (3): Laboratory findings among studied groups:

The mean total platelet count level of the patients were 95.80±77.79, 57.66±47.06,41.62±21.69, in groups D,DW and SD, respectively (P<0.05). For patient with groups D,DW, and SD, mean AST values were, 55.50±14.40, 80.00±15.80 and 130.00±15.80 respectively (P<0.05) and mean ALT values were, 47.90±10.30, 76.10±11.60,and 110.00±11.80 respectively (P < 0.05). From 100 specimens 20% positive for primary infection (IgM) and 80% of specimens were positive for secondary infection (IgM and IgG).

Figure (2): Showing platelet count in different categories of dengue:

Thrombocytopenia at level of 41-50,000 were found in 6(24%) of group D and 28(46.7%) of group DW compared to 8(53.3 %) of group SD (P<0.05).

Table (4): Logistic regression analysis on association between clinical profiles and severe dengue fever:

Patient with persistent vomiting (OR 5.72, 95% CI 1.76 to 18.60, p-value 0.003), abdominal pain (OR 5.01, 95% CI 1.06 to 23.58, p-value 0.041), jaundice (OR 21, 95% CI 2.01 to 218.58, p-value 0.01), hepatomegaly (OR 5.58, 95% CI 1.75 to 17.75, p-value 0.003), ascites (OR 9.93, 95% CI 1.95 to 50.42, p-value 0.005), and pleural effusion (OR 10.12, 95% CI 2.32 to 44.02, p-value 0.002) were associated with severe dengue infection.

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Discussion :

Dengue has a wide spectrum of clinical present. The classification into levels of severity has a high potential for being of practical use in the clinicians' decision(2).

In the present study, it was found that higher percentage of infection was in males than females and child ages group 11 -14 years than other groups. These data are in accordance with those reported in other studies (6,7). These results could be explained by the fact that male clothes in hot areas which make their bodies more exposure, meanwhile, females wear heavy clothes and cover most of their body, protecting them from mosquito bites, and they are culturally less likely to be outside the home compared with their male counterparts.

The highest percentage of cases were found to be group DW (60%), followed by group D (25%) and group SD (15%).These findings are similar with those reported in other studies (8,9).Meanwhile, Narvaez et al, found rates of both DW and SD to be similar and high in percentage (48% and 44%, respectively) than group D(4). Gan et al, found group D to be the most frequently occurring classification (48%), followed by DW (36%) and SD (16%) (10).These differences could be due to different sample size between these studies and ours.

The percentage of cases with dengue infection was significantly higher in urban than in rural areas. These data are consistent with other studies (11,12).The water supply system in urban was daily interrupted so many houses keep or store water for daily use in tanks,water storage container. Barde et al, observed that the water storage containers were the main sources of vector breeding sites for dengue virus activity. These breeding sites were responsible for mosquito prevalence (13).

In the current study, it was observed that persistent vomiting was significantly higher in group DW and group SD compared to group D. This study also showed that persistent vomiting was associated with

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severe dengue infection in children (OR 5.72, 95% CI 1.76 - 18.60) (Tables 2 and 4).These findings are similar with those reported in other studies (14,15). Persistent vomiting with dengue infection was associated with higher risk for severe dengue infection(16). A Brazilian study showed persistent vomiting was associated with death in children with severe dengue virus infection, so more attention should be given in children with persistent vomiting in early dengue virus infection (17). It was found that the abdominal pain was significantly higher in group DW and group SD compared to group D. This study also showed that abdominal pain was associated with severe dengue infection in children (OR 5.01, 95% CI 1.06 - 23.58) (Tables 2 and 4).These data are in accordance with those reported in other studies (14,18,19). Alexander et al, in a multicenter study conducted in four Latin American and Southeast Asian countries, demonstrated that abdominal pain was associated with a significantly higher risk of severe illness(20). Acute abdominal pain is a common symptom in dengue infection and occasionally misdiagnosed as acute appendicitis; can have diverse etiology ranging from flavi virus associated hepatitis, acalculous cholecystitis and shock (21).

It was observed that jaundice was higher in group SD compared to group D and group DW. This study also showed jaundice was associated with severe dengue infection (OR 21, 95% CI 2.01-218.58) (Tables 2 and 4).This is consistent with several studies (14,22,23). A study from India reported a 15% occurrence of jaundice with dengue infections.(24).The degree of liver dysfunction in children with Dengue virus infection varies from mild injury with an elevation of transaminase activity to severe injury with jaundice (25). It was also found that hepatomegaly was significantly higher in group DW and group SD compared to group D. This study also showed hepatomegaly was associated with severe dengue infection (OR 5.58, 95%CI 1.75- 17.75) (Tables 2 and 4).Similar findings are been observed by others (11,26,27). Hepatomegaly in dengue has been reported in 43-100% of cases in children (28), it is due to direct

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involvement of dengue virus in the liver (29). Liver size in children used a limit of ≥3 cm in children under 5 years because smaller children with palpable liver size up to 2 cm may be found in normal conditions(15).This result showed an enlarged liver requires special attention in children with dengue virus infection. It was observed that ascites was significantly higher in group DW and group SD compared to group D. This study also showed ascites was associated with severe dengue infection in children (OR 9.93,95%CI 1.95 -50.42) (Tables 2 and 4).These data are in accordance with those reported in other studies (11,14,15). It was also observed that pleural effusion was higher in group SD compared to group D and group DW. This study also showed pleural effusion was associated with severe dengue infection in children (OR10.12,95%CI 2.32 - 44.02) (Tables 2 and 4).This is consistent with several studies (11,19,30).The basic pathophysiologic mechanism in severe dengue infection is the plasma leakage which occurs due to increased capillary permeability that caused by endothelial dysfunction due to immune mediators and endothelial cell injury occurring in more severe disease.Generally, the plasma leakage occurs selectively into peritoneal and pleural spaces (31).Sahana and Sujatha, found that ascites and pleural effusion were significantly high in severe dengue cases which can be used as possible markers of severe dengue (7). Shock was present only in SD. This is consistent with several studies(9,14,15). Shock occurs when a critical volume of plasma is lost through leakage (2). Central nervous system (CNS) involvement in the form of altered sensorium was seen only with three patients in SD group. This result was similar to those reported in other studies (8,32).The neurological manifestations are due to neurotrophic effect of the dengue virus related to the systemic effects of dengue infection and immune-mediated (11).

It was observed that the mean platelet count levels were significantly lower in Group DW and Group SD compared to group D. It was also found that the percentage of cases with thrombocytopenia at level of 41-50,000 were significantly higher in Group DW and

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Group SD compared to group D. These data are in accordance with those reported in other studies (7,14,15). Different mechanisms have been explain DENV-associated thrombocytopenia, including the suppression of bone marrow and the peripheral destruction of platelets.(33).

The AST and ALT levels were significantly higher in Group SD compared to group D and DW which is similar to other studies (34,35).The AST and ALT levels were significantly higher with increasing dengue severity by both 1997 and 2009 WHO criteria. (36). The mechanisms of liver injury in dengue may be due to direct effects of the virus or host immune response on liver cells, circulatory compromise, metabolic acidosis and/or hypoxia caused by hypotension or localized vascular leakage inside the liver (24).

Out of the 100 specimens, 20% were positive for primary infection (IgM) and 80% were positive for secondary infection (IgM and IgG). This result is similar to those obtained by others (4,6,37).The proportion of dengue virus of chronic infections was found more than acute infections which indicated the prevalence of dengue fever outbreaks for quite some time and background endemicity preceding an outbreak(38).

CONCLUSION: Dengue fever had a constellation of symptoms and signs and investigations. A high index of suspicion in endemic areas was important and helped us in identifying sick dengue cases early.

Table (1): Demographic data of studied groups

Variables	Group D	Group DW	Group SD	Total	P. value
<1 year	-	1(1.7%)	-	1(1%)	0.417
1-5 years	2(8%)	14(23.3%)	3(20%)	19(23%)	
6-10 years	10 (40%)	20(33.3%)	4(26.7%)	34(34%)	
11-14 years	13 (52%)	25(41.7%)	8(53.3%)	46(46%)	

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Male	16(64 %)	35(58.3%)	9(60%)	60(60%)	0.0001
Female	9(36%)	25(41.7%)	6(40%)	40(40%)	
Urban	14(56%)	33(55%)	9(60%)	56(56%)	0.015
Rural	11(44%)	27(45%)	6(40%)	44(44%)	

Table (2):Clinical characteristics of the studied groups

Variables	Group D	Group DW	Group SD	Total	P. value
Fever	25(100%)	60(100 %)	15(100 %)	100(100%)	0.397
Headache	23 (92%)	57 (95%)	14(93.3%)	94(94%)	0.906
Aches and pains	11(44%)	24(40%)	7 (46.7%)	42(42%)	0.383
Periorbital pain	15(60%)	35(58.3%)	10(66.7%)	60(60%)	0.568
Persistent vomiting	-	22(36.7%)	10 (66.7 %)	32(32%)	0.042
Abdominal pain	3(12%)	45(75%)	13(86.7%)	61(61%)	0.0001
Jaundice	-	1(1.7%)	3(20%)	4(4 %)	0.020
Hepatomegaly	-	18(30%)	9(60%)	25(25%)	0.036
Splenomegaly	-	3(5%)	1(6.7%)	4(4%)	0.797
Ascites	-	3(5%)	4(26.7%)	7(7%)	0.020
Pleural effusion	-	4(6.7%)	5(33.3%)	9(9 %)	0.009
Dyspnea	-	3(5%)	2(13.3%)	5 (5%)	0.265
Shock	-	-	2(13.3%)	2 (2%)	0.048
Lethargy/ restlessness	-	15(25%)	5(33.3%)	20(20%)	0.515

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Impaired consciousness	-	-	3(20%)	3(3%)	0.012
Mucosal bleeding	-	7(11.7)	2(13.3%)	9(9%)	0.183
Sever bleeding	-	-	1(6.7%)	1(1%)	0.319
Maculopapular rash	4(16%)	12(20%)	2(13.3%)	18(18%)	0.556
Petechial rash	3 (12%)	9(15%)	3(20%)	15(15%)	0.637
Multiple organ failure	-	-	1(6.7%)	1(1%)	0.319
Positive tourniquet test	10(40)	23(38.%)	5(33%)	38(38%)	0.753

Table 3: Laboratory findings among studied groups

Variables	Group D	Group DW	Group SD	P.value
Mean hemoglobin (g/dl)	9.52±1.69	9.35±1.60	8.9±1.44	0.243
Mean WBC(cells x 10^9/L)	3600±3236.12	4269.66±4185.55	4013.33±3920.79	0.720
Mean platelet count (cell ×1000/cm^3)	95.80.±77.79	57.66±47.06	41.62±21.69	0.0124
HCT (%)	39.56±4.17	40.98±2.25	41.73±1.67	0.062

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AST (IU/L)	55.50±14.40	80.00±15.80	130.00±15.80	0.0001
ALT(IU/L)	47.90±10.30	76.10±11.60	110.00±11.80	0.0001
Primary infection IgM	5(20%)	13(21.7%)	2(13.3%)	0.844
Secondary infection(IgM and IgG)	20(80%)	47(78.3%)	13(86.7%)	0.488

Table 4: Logistic regression analysis on association between clinical profiles and severe dengue fever

Variables	Odds ratio	95 % CI:	P. value
Persistent Vomiting	5.72	1.76 to 18.60	0.003
Abdominal pain	5.01	1.06 to 23.58	0.04
Jaundice	21	2.01 to 218.58	0.01
Hepatomegaly	5.58	1.75 to 17.75	0.003
Ascites	9.93	1.95 to 50.42	0.005
Pleural effusion	10.12	2.32 to 44.02	0.002

Figure (1): Percentage of dengue cases severity

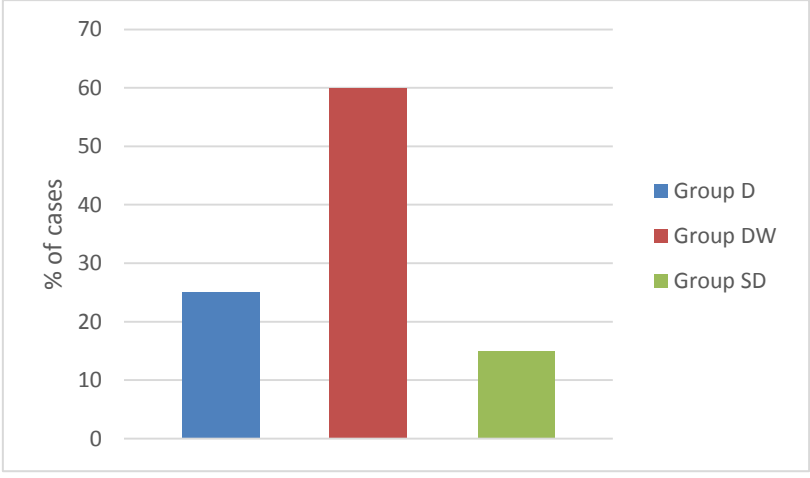

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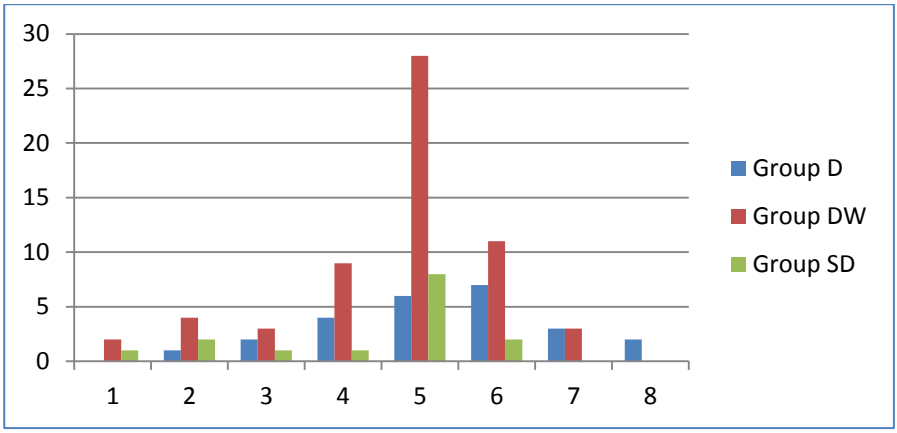
Figure (2): Platelet count in different categories of dengue.



Platelet Count grades: 1= <10,000; 2=11,000–20,000; 3= 21,000–30,000; 4=31,000–40,000; 5=41,000 – 50,000; 6= 51,000 –100,000; 7=101,000–150,000; 8= >150,000 .

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