

Paper

Accuracy of selected indicators in leaking for the management of dengue haemorrhagic fever

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Abstract

Aims: Conventional clinical and laboratory parameters for the management of dengue haemorrhagic fever (DHF) were validated using ultrasound scan (USS) as the gold standard.

Methods: Clinically suspected 184 patients with platelet count <100,000 were enrolled in the study.

Results: USS evidence of leaking was observed in 48% of the sample. When Hct rises >10% and >20% were used as a predictor of leaking, sensitivity and specificity of 30%, 82% (PPV 60%, NPV 56%) and 11%, 94% (PPV 63% and NPV 54%) were observed. Liver tenderness and gall bladder wall oedema (wall thickness>6mm) had sensitivity of 28%, 91% and specificity of 83% and 94% as predictors of leaking. Haematocrit rise > 10% during any stage of critical phase associated with 94% sensitivity and 37% specificity (PPV 46%, NPV 92%) in prediction of complications.

Conclusions: Rising HCT, liver tenderness and clinical detection were found to be weak predictors of onset of leaking. HCT rise was a strong predictor of complications during the leaking phase.

risk of dengue haemorrhagic fever (DHF). The proportion of dengue patients going in to DHF, and the outcome greatly varies according to virus serotype, geographic region and host factors⁴.

Third space fluid accumulation (TSFA) or leaking is the hallmark of DHF⁴, where in ward close monitoring is essential in order to prevent death. Accurate detection of the onset of leaking phase is one of the most difficult tasks in day to day practice in dengue fever management in busy medical units. Detection of leaking in a dengue patient is mainly a clinical diagnosis. This clinical diagnosis is supported by several investigations and clinical signs such as platelet count (less than $100 \times 10^3/\mu\text{l}$), Hematocrit (Hct) rise and liver tenderness^{4,5}. Detection of ascites and pleural effusion by ultrasound scan (USS) is considered as the gold standard in identification of leaking as all other predictors of leaking are inaccurate, variable and subjective⁵.

The hematocrit changes can be due to many other conditions like dehydration, smoking, hypoxia etc⁵. Over hydration with oral or parental fluids on the other hand artificially reduce the rising Hct⁵. Concealed bleeding among dengue shock patients (in leaking phase) is associated with inappropriately low Hct and results in improper management. Based on clinicians observations, a rising WBC also is suggested as an indicator of leaking but this is not properly validated. Although liver tenderness is a simple clinical sign during examination, it is very nonspecific and present in many other causes of hepatitis.

Facilities for ultra sound scan for every dengue patient is not available in many medical units in Sri Lanka. Therefore, clinicians have to depend on their clinical experience and other subjective investigations such as rising Hct to identify and manage DHF in day to day practice. Furthermore, many of ultrasonically detected dengue leaking patients eventually recover without causing any of significant complications and only few patients experience serious outcomes. Therefore, it is important to find out clinical and laboratory parameters to monitor patients during leaking phase for early identification of complications and to reduce the mortality rate and the burden on health care professionals.

Introduction

Dengue fever (DF) is caused by any of four closely related viruses, or serotypes: dengue virus 1-4^{1,2}. Infection with one viral serotype does not induce protective immunity against other dengue viral serotypes³. Secondary dengue infections increase the

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Methods

The study was a prospective cross-sectional study carried out for a period of a year (2015-2016) in medical wards in Base Hospital, Horana. Ethical approval was granted by the National Institute of Health Science (NIH), Sri Lanka (NIHS/ERC/16/29). One hundred and eighty four dengue suspected patients were included for the study diagnosed according to 2012 National guideline³. Informed written consent was obtained from the patients.

Case definition – Dengue illness (DF/DHF) was considered in the differential diagnosis of patients presenting with acute onset of fever with two or more following: headache, retro-orbital pain, myalgia, arthralgia, rash (diffuse, erythematous, macular) hemorrhagic manifestation (petechiae, positive tourniquet test) with leukopaenia ($<5 \times 10^3/\mu\text{l}$), platelet count, $<150 \times 10^3/\mu\text{l}$ and rising of haematocrit by 5-10%⁵. Such patients were clinically diagnosed as suspected dengue patients and selected for this study after obtaining the written consent when their platelet count was $<100 \times 10^3/\mu\text{l}$.

Study population was subjected to ultrasound scan twice daily. Abdominal ultrasound was performed on a Toshiba Xario 100 (TUS-X100) unit, equipped with a 6C1 wide bandwidth (3.0-5.0 MHz) convex probe and 11L4 wide bandwidth (7 to 12, MHz) linear probe. The abdominal ultrasound was done in all cases after 4 or more hours of fasting for better visualization of the gall bladder. A consultant radiologist who is a member of this study performed all the serial ultrasound examinations till the end of critical phase. Hct and full blood count were measured after 3-4 hours of ultrasound scan. Clinical diagnosis of leaking was obtained after discussion with dengue management clinical team irrespective of the result of ultrasound scan.

Demographic and clinical details of the patients were recorded using a pre tested questionnaire. The statistical analysis was carried out by using the software, Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 17.0. Descriptive statistics were represented as a percentage (%) value. The statistical tests for qualitative variables were carried out using the chi-square test (χ^2 test). All these tests were two sided. The level of significance was taken at 5% ($p < 0.05$).

Results

Of the 184 patients 113 (61%) were females and 71 (39%) were males. The mean age of the study cohort was 40 ± 17.3 years. Ultrasound scan evidence of

leaking was observed in 48% (88/184) of dengue suspected patients who had a platelet count less than $100 \times 10^3/\mu\text{l}$.

The duration of fever when patients start leaking were tabulated in table 1.

More than 10% Hct rise from base line was observed in 30% (26/88) of patients and over 20% rise was seen in 11% (10/88) of ultrasonically confirmed leaking patients in the first four hours of leaking (Table 2).

When $>10\%$ Hct rise from baseline was used as a predictor of leaking, against USS scan within four hours it showed 30% sensitivity and 82% specificity (PPV 60%, NPV 56%) whilst $>20\%$ Hct rise showed 11% sensitivity and 94% specificity (PPV 63% and NPV 54%).

Liver tenderness was observed in 28% (25/88) of patients within early hours of leaking. The overall clinical judgment of leaking irrespective of the ultrasound scan was observed in 29.5% (26/88) of leaking patients (Table 3).

Liver tenderness had a sensitivity and specificity of 28% and 83%. Clinical judgment of leaking had a sensitivity and specificity of 30% and 89%.

Gallbladder wall oedema was considered when gall bladder wall thickness was over 6 mm for this study. Gallbladder wall oedema was observed in a total of 86 patients. Of them 80 patients had leaking. When gallbladder wall thickness of more than 6 mm was considered as a predictor of leaking a sensitivity and specificity of 91% and 94% (PPV 93% and NPV 92%) were observed (Table 4).

Although nearly 50% patients had leaking according to ultrasound scan 1/3 of them were managed with hourly fluid replacement not exceeding 100ml at any stage without a rise in Hct, reduction of urine output or any other complications. Serial ultrasound scans did not show any evidence of progression of leaking. There were 9 patients with pre shock and all were having leaking. They were successfully managed with fluid boluses (both normal saline and dextran). Hematocrit rise $>10\%$ during any stage of critical phase was associated with 94% sensitivity and 37% specificity (PPV 46%, NPV 92%) in the prediction of complications (shock, pre shock, reduction of urine output for less than 0.5 ml per kilogram body weight for two hours, and those who needed fluid boluses >200 per hour). The association between complications and hematocrit rise $>10\%$ is represented in Table 5.

Table 1. The duration of fever days when patients start leaking (total leaking patients n=88)

Number of fever days	D-1	D-2	D-3	D-4	D-5	D-6	D-7	D-8
Number of patients	0	02	30	36	12	06	02	0

D: Day

Table 2. Association between HCT rise and the leaking

		<i>Leaking</i>			<i>P value</i>
		<i>Yes</i>	<i>No</i>	<i>Total</i>	
Hct rise	Nil	62	79	141	0.162
	10-20%	16	11	27	
	>20%	10	6	16	
	Total	88	96	184	

Table 3. Association between liver tenderness, clinical judgment and the leaking

		<i>Leaking</i>			<i>P value</i>
		<i>Yes</i>	<i>No</i>	<i>Total</i>	
Liver tenderness	No	63	80	143	0.056
	Yes	25	16	41	
	Total	88	96	184	
Clinical judgment of leaking	No	62	85	147	0.002
	Yes	26	11	37	
	Total	88	96	184	

Table 4. Association between gall bladder wall oedema and the leaking

		<i>Leaking</i>			<i>P value</i>
		<i>Yes</i>	<i>No</i>	<i>Total</i>	
Gall bladder wall oedema >6 mm	No	8	90	98	0.000
	Yes	80	6	86	
	Total	88	96	184	

Table 5. Association between complications and hematocrit rise >10%

		Hematocrit rise > 10%			<i>P value</i>
		<i>> 10%</i>	<i>< 10%</i>	<i>Total</i>	
Complication	No	2	23	25	0.000
	Yes	33	39	72	
	Total	35	62	97	

Out of 88 patients with leaking 50 (57%) were afebrile when leaking started, and 19 (21.5%) had fever for less than a day during the critical phase. Another 19 (21.5%) leaking patients had continuous fever during the leaking phase.

In the study population any detectable change in pattern of white blood cells (WBCs) was not observed at the beginning of critical phase.

Discussion

Nearly 50% of study population had USS evidence of leaking. This is a relatively higher proportion compared to previous reports⁶. A previous study done in (2004-2006) Sri Lanka had reported nearly 16% DHF cases among 357 DF patients⁶. Another study done in Sri Lanka in 2013, including 102 dengue patients with platelet count less than $100 \times 10^3/\mu\text{l}$ found 41% had leaking⁷. This is evidence for variable and unpredictable nature of dengue infections and increasing trend of secondary infections over time⁷.

In this study, we selected clinically suspected dengue patients with platelet count less than $100 \times 10^3/\mu\text{l}$.

All of them underwent serial USS scans twice daily followed by haematocrit assessment and clinical assessment to identify leaking. Conventional methods such as rising Hct, liver tenderness and clinical judgement were weak predictors of onset of leaking. Although they showed low sensitivity (30%) it had relatively higher specificity. It is clear that conventional methods are weak predictors of leaking and can miss many DHF patients in early hours of onset of the leaking.

In the present study gall bladder wall oedema was considered when thickness of the gall bladder exceeds > 6mm. Gall bladder wall thickness of more than 3 mm is a nonspecific finding in many conditions including dengue fever as well as DHF⁸. It has been previously reported that around 30% DF patients can present with gall bladder wall oedema > 3mm and wall thickness increase markedly among patients with severe dengue^{8,9,10}. However when gall bladder wall oedema is more than 6 mm it associated with 91%, 94% sensitivity and specificity respectively. Based on the results gall bladder wall oedema exceeding > 6 mm was found to be a good predictor of leaking in DHF rather than 3 mm.

In the study over one third of patients with ultra sound evidence of leaking didn't show any progression in leaking or complications such as reduction in urine output or pre shock. All of them were managed with hourly fluid requirement not exceeding 100ml and all of them were clinically well during entire critical phase. Therefore it is not clear whether these patients belong to a separate category "pseudo leakers" or real DHF patients with mild short lasting fluid leakage. In a busy medical ward these patients have to be monitored hourly as such patients are categorized under DHF. Based on the results of the present study although serial ultrasound scans are found to be very useful in detecting the onset of leaking it seems there were possible overestimations.

Hct rise >10% during critical phase was found to be a strong predictor of complications as it showed 94% sensitivity in predicting the patients with complications including those who needed fluid boluses more than 200ml an hour. Therefore, rising haematocrit can be used to monitor patients during critical phase.

Conclusion

Based on the finding of this study conventional methods such as rising haematocrit were found to be weak predictors of detection of leaking. However they can be successfully used to monitor DHF patients during critical phase to identify complications.

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