

Repeated Tourniquet Testing as a Diagnostic Tool in Dengue Infection

O Norlijah, MRCP*, A Nor Khamisah, MDUPM**, A Kamarul, M Paeds*** S Mangalam, FRCPath****

*Faculty of Medicine and Health Sciences, University Putra Malaysia, **Ministry of Health, Malaysia, ***Institute of Paediatrics, Hospital Kuala Lumpur, ****Department of Pathology, Hospital Kuala Lumpur, Malaysia

Summary

Prospective evaluation of repeated standard tourniquet testing as a diagnostic indicator of dengue infection was done. Included were patients admitted to a children's hospital in Kuala Lumpur on a clinical suspicion of dengue infection based on the World Health Organization (WHO) criteria. A standard method of tourniquet was performed on 79 patients on a daily basis following admission. Out of 79 subjects, tourniquet tests were positive in 65 subjects and negative in the remaining 14 subjects. Fifty-eight subjects were serologically confirmed cases, 4 indeterminate and the remaining 17 subjects had negative serology. For diagnostic classification, 13 had dengue fever, 49 with dengue haemorrhagic fever (DHF) while 17 had non-dengue infection. The sensitivity and specificity of the tourniquet test was 82.8% and 23.5% respectively. The positive predictive value (PPV) was 78.7% while the negative predictive value (NPV) was 28.6%. In addition, the tourniquet test aided in the diagnosis of one-fifth of patients with DHF, who presented with a positive tourniquet test as the only bleeding manifestation. It seems that in a hospital setting, the tourniquet test adds little to the diagnosis of dengue infection/DHF. A positive tourniquet test, repeatedly performed, was found clinically useful as a preliminary screening test in dengue infection as recommended by WHO. However, it was not very specific and had a high false positive rate.

Key Words: Dengue infection, Dengue haemorrhagic fever (DHF), Tourniquet test

Introduction

The geographical spread, incidence and severity of dengue fever (DF) and dengue haemorrhagic fever (DHF) are increasing in the Americas, South-East Asia, the Eastern Mediterranean and the Western Pacific. Some 2,500 million to 3,000 million people live in areas where dengue viruses can be transmitted. It is estimated that 50 million infections occur each year, with 500,000 cases of DHF and at least 12,000 deaths¹. The hallmark that differentiates DHF and dengue fever is the increased capillary permeability and haemocoagulation in DHF. Increased capillary leakage will result in plasma leakage and subsequent hypotension². Thrombocytopenia, coagulation

abnormalities and clinical bleeding of varying severity are features of DHF and DSS, but may also occur in DF³.

The tourniquet test has been recommended as the initial screening procedure of patients with suspected DHP⁴. This 5 to 10 minute platelet-activity haemostasis test is to assess fragility of capillary walls and to evaluate platelet number and function. The World Health Organisation (WHO) indicated a positive tourniquet test as an important clinical manifestation particularly in DHF grade I. Previous studies have evaluated the role of tourniquet test in dengue infection, performed as a single testing at the time of first presentation; and showed that it was specific and had a high positive predictive value but was not

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Corresponding Author: Norlijah Othman, Department of Human Growth & Development, Faculty of Medicine & Health Sciences, UPM 50586 Jalan Masjid, Kuala Lumpur

sensitive^{5,6}. However, there is a dearth of data on the formal evaluation of repeated, frequent tourniquet testing as a diagnostic utility for dengue infection. The aim of this study was to evaluate the validity of repeated tourniquet test as an indicator of dengue infection.

Materials and Methods

Subject enrollment

Previously healthy children presented to a tertiary children's hospital in Kuala Lumpur between June and August 2001 were eligible for entry into this study if they met the following criteria: age between 6 months and 12 years, a clinical suspicion diagnosis of dengue infection/DHF using WHO criteria at initial presentation on admission. The provisional diagnosis of DHF was made in all of the cases based on clinical assessment, which comprised of patient's symptoms and examiner's findings. Informed verbal consent was obtained from parents or legal guardians of each child before enrolment.

Study design

At the time of admission to the hospital, subjects and their parents were interviewed to collect demographic data and medical history. The tourniquet test was carried out by NKA, a third-year medical student, on alternating arms each day for all subjects from the time of enrolment. An appropriate sized blood pressure cuff was chosen according to the length of the upper arm of the subject. The cuff was then inflated to a point midway between the diastolic and systolic pressure and maintained for the next 5 minutes. The number of petechiae that appeared on the flexor aspect of the forearm just distal to the antecubital fossa was determined. As stipulated by the WHO criteria, the test was considered positive when 20 or more petechiae per 2.5cm (1 inch) square were observed after the tourniquet was released³. If the test was negative, the test would be repeated the next day until the subject was discharged from the hospital or until > 20 petechiae were recorded on any one day. Children presenting with shock were resuscitated first with parenteral fluids and the tourniquet test was performed after adequate circulation had been achieved.

The clinical and laboratory results were recorded in standardized data notes and later transferred to a computer database. In this study, the results of the tourniquet tests were not validated by a second independent operator.

Dengue serology

Serum samples for dengue serology were obtained from all children at the time of admission. The specific antibody is based on a monoclonal antibody capture enzyme immunoassay (MAC-EIA), which has excellent specificity and sensitivity, comparable to haemagglutination-inhibition test, the gold standard for dengue serological diagnosis. The detection of dengue specific IgM antibodies, which are produced in both primary and secondary dengue infections, indicates active or recent infection.

Case definitions

Patients with positive serology but did not satisfy WHO criteria for DHF were considered to have dengue fever. A diagnosis of DHF was assigned following the WHO clinical definition on the basis of the presence of plasma leakage and thrombocytopenia of less than or equal to 100,000/mm^{3,4}. Evidence of plasma leakage could include a peak hematocrit value of >20% above the value at admission or discharge, clinical evidence of pleural effusion or detection of ascitis on physical examination. The serologic data was not used to assign the clinical diagnosis of DHF. Patients with definitive negative serology and who did not fulfill the WHO criteria for DHF, were considered not to have dengue infection.

Data analysis

The data was analyzed using Statistical Package for Social Science (SPSS) version 10.0 software. The criterion for determining the presence and the absence of the dengue infection was based on confirmation by a serological diagnosis of dengue IgM. A positive dengue infection constitutes a positive dengue IgM, while a negative dengue IgM represents no infection. Therefore, cases with indeterminate status in dengue serology were excluded. The outcome variable in this study was confirmed dengue cases. The other variables were tourniquet test and dengue IgM serology results. While dengue IgM results confirmed the dengue cases, the tourniquet test was evaluated for its validity and/or reliability as a prescriptive screening tests for dengue infection. The measurement of sensitivity and specificity were used for evaluating the validity of the tourniquet test. Sensitivity of the test is defined as the ability of the tourniquet test to identify correctly those who have dengue infection; on the other hand, specificity denotes the ability of the test to ascertain correctly those who do not have dengue infection. The positive predictive value (PPV) of a positive test result is the probability that a patient who gives a positive test

has a disease and the predictive value of a negative result (PNV) is the corresponding probability that a patient with negative result does not have the disease.⁷

Results

Between June and August 2001, 79 subjects were admitted for suspected dengue infection and thus considered into the study. The overall male to female ratio was 1.6:1, and the mean age of the subjects was 6.1 SD±2.9 years and ranged from 0.5 to 11.6 years. The majority of the subjects were Malays (73, 92.4%), followed by three Chinese and Indians respectively. The average duration of fever before entry period was 5 days.

Of these 79 subjects, serologically positive dengue IgM was found in 58 subjects, indeterminate status in four, and negative serology in the remaining 17 subjects. In the indeterminate cases, a second sample was not obtained or the first sample was obtained too early for definitive serodiagnosis. For diagnostic classification, 13 of the 79 subjects had dengue fever, 49 had DHF while the remaining 17 had non-dengue infection. Of the 49 subjects with DHF, 4 had indeterminate serology while 45 had positive dengue IgM.

The tourniquet test was found to be positive in 65 out of 79 subjects, including 4 subjects with indeterminate serology. The results of the tourniquet test in the various diagnostic categories are illustrated further in Figure 1. Slightly more than 80% of these patients were found positive after day four of fever, specifically between day five to eight. This coincided with a day or two prior to development of shock in DHF.

In the DHF group with positive tourniquet test, there were 9 patients in DHF grade 1, 12 in grade II and 20 in grade III. On the other hand, in the negative tourniquet test group, there was 1 in DHF I, 3 in DHF

II, 3 in DHF III and 1 in DHF IV. Bleeding manifestations were seen in both dengue fever and DHF. Three patients with dengue fever presented with petechiae (2) and gum bleeding (1). Tourniquet test was the only manifestation of bleeding in 9 subjects with DHF. In this group of patients, the tourniquet test provided additional information to aid diagnosis of DHF and this represented 18% of DHF in the study.

The tourniquet test gave positive results in 66% of patients with confirmed dengue infection. The test was almost as frequently positive in dengue fever (11 out of 13) as those with DHF (37 out of 41 serologically confirmed subjects).

Evaluation of tourniquet test in dengue infection

For the above purpose, only serologically confirmed cases were included. Hence, a total of 75 subjects were analyzed, excluding 4 with indeterminate serology.

As shown in Table I, 48 were true positives while true negatives were found in 4 subjects. In the remaining 23 patients, 13 and 10 subjects had false positives and false negatives, respectively.

The validity of the tourniquet test as an indicator for dengue infection was further evaluated. Table II shows the sensitivity, specificity and predictive values of the tourniquet test in the diagnosis of dengue infection.

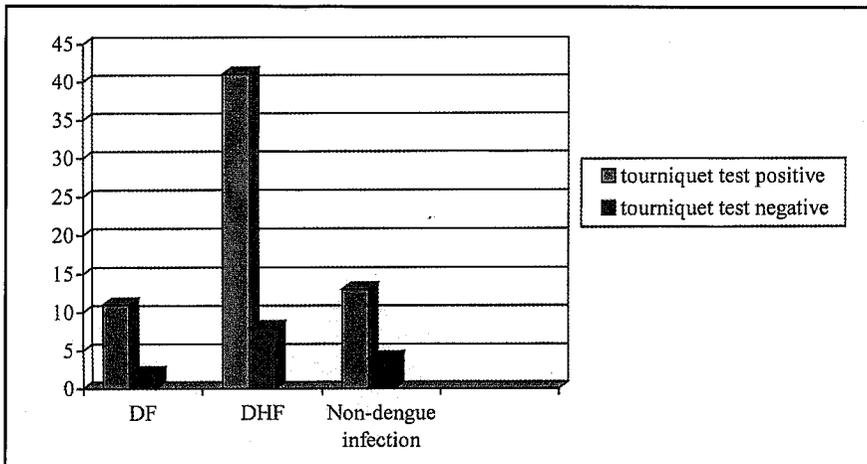
Table II shows that the sensitivity of tourniquet test in the diagnosis of dengue infection was 82.8% and percentage of false negatives (which is complementary to sensitivity) was 17.2%. The results also showed that the specificity of the tourniquet test was 23.5% and percentage of false positive was 76.5%. Therefore the use of repetitive tourniquet test in the diagnosis of dengue infection resulted in a high false positive rate.

Table I: Validity of Tourniquet Test in Dengue Infection

	Dengue IgM		Total
	Present	Absent	
Tourniquet test positive	48	13	61
Tourniquet test negative	10	4	14
Total	58	17	75

Table II: Predictive values of tourniquet test in the diagnosis of dengue infection

	Tourniquet test
Sensitivity	82.8%
Specificity	23.5%
Positive predictive value	78.7%
Negative predictive value	28.6%

**Fig 1: Results of Tourniquet Test in Various Diagnostic Categories**

Discussion

Many children with suspected dengue infection are not admitted to a hospital facility but rather to a health clinic or community practitioner where laboratory facility to monitor a blood count is not available. In these centres, a tourniquet test plays as an important initial screening procedure for patients with suspected dengue infection. A positive tourniquet test is considered as the only haemorrhagic manifestation in grade 1 DHF.

Haemorrhagic manifestation is one of the essential criteria in the diagnosis of DHF. According to WHO classification of DHF, haemorrhagic diathesis of at least a positive tourniquet needs to be present⁴. In this study, 18% of DHF patients presented with positive results in tourniquet test as the only bleeding manifestation. In other words, the test provided additional information in the diagnosis of DHF in the study. It should be borne in mind that the population was a highly selected patient, in that the children were thought to have dengue infection and were ill enough to warrant admission. In addition, the study was conducted in an endemic area and during the peak season of dengue infection.

In this study, in which quite a proportion of patients had dengue infection, repeated tourniquet testing was found to be not specific but reasonably sensitive. In addition, it gave rise to a fairly high PPV of 78.7% but at the same time was a poor negative predictor for dengue infection. This study was carried out during the peak epidemic season of the year where dengue was the main cause of admission. This was further corroborated by the presentation of dengue infection in three-quarter of the study population; and two-third of those with dengue infection had DHF. An earlier study found that a positive standard tourniquet test repeatedly and serially performed yielded a lower PPV of 67% and a correspondingly lower sensitivity, and a fairly higher NPV (72%)⁹. It should be noted that in that study, the proportion of patients without dengue infection was one and a half time more compared with dengue infection. Differences in the design of these studies, noted above, are likely to explain the differences in findings.

In comparison to other studies where tourniquet test was performed once at the time of presentation in a population of dengue/DHF patients, this study showed that repeated and serial tourniquet testing had an

adverse effect to sensitivity and specificity values to a single tourniquet testing^{5,6}. Phuong et al in a large prospective study on evaluation of the standard tourniquet test of 548 serologically confirmed dengue infection of hospitalised children found a high specificity and positive predictive values of 94.4% and 98.3% respectively but sensitivity of 41.6% only⁵. Similarly, in a study to evaluate the predictive value of clinical and laboratory findings for dengue infection/DHF in Thailand, a tourniquet test of more than 10 petechiae combined with a flushed face and no coryza, which were used as enrolment criteria in that study, had a specificity and positive predictive values of 97.1% and 97.2% respectively⁶. However, in the latter study, no mention was made on the sensitivity.

The difference in findings could not be explained alone by the repeated versus single tourniquet testing. Other factors such as enrolment criteria and difference in methodology adopted could elucidate the differences in findings. For the current study, the serology for dengue was not repeated on discharge from the hospital. As a consequence, the positive predictive value was not as high as achieved in previous studies.

This study agrees with suggestions made by Phuong *et al*,⁶. Following admission, repeated tourniquet testing performed on children suspected to have dengue from an endemic area during an epidemic season, improved its sensitivity. On the other hand it also generated more false positive results and one possible reason for this is repetitive tourniquet test performed on a daily basis on the same site will induce trauma to capillaries.

In the present study, we found that children with dengue infection were more likely to have positive tourniquet test, compatible with other studies^{5,6,8,9}. It was almost frequently found positive in both dengue fever and DHF. The test was a poor differentiator between DHF and dengue fever.

We also found that tourniquet test was occasionally positive in non-dengue infections. This pattern of results was similar to that seen in several previous studies looking at tourniquet test in dengue infection. Kalayanaroj et al found 23 of 108 (21%) children diagnosed with other febrile illness without a specific bacteriological cause and negative dengue serology had a positive tourniquet test⁹. Although positive tourniquet test suggested dengue infection, it could be caused by other factors. Tourniquet test is a test of integrity of capillary vessels and platelet function as

well as numbers. Other diseases such as scurvy, disseminated intravascular coagulation, chronic idiopathic aplastic anaemia, von Willebrand's disease, anaphylactoid purpura, thrombocytopaenic purpura and non-thrombocytopaenic purpura which affect any of the above features may also present with positive tourniquet test^{10,11}.

We also found that the tourniquet test was positive if the test was performed after day four of illness, specifically between day five to eight. This was related to the progression of the disease involving initially capillary damage, followed by platelet deficiency and dysfunction, and followed still later by defects in blood coagulation. In DHF, capillary damage develops in the early days of illness, and positive tourniquet test and petechiae are early evidence of bleeding³.

In this study, children presenting with dengue shock syndrome, were resuscitated first before the tourniquet test were performed. It is a known phenomenon in DHF that as the disease progresses, tourniquet test becomes negative when performed during the hypotensive episode. However, after restoration of depleted intravascular volume the test may become positive^{8,12}.

Although the tourniquet test has been claimed to be a simple, convenient and readily available diagnostic tool, it has limitations such as causing a degree of discomfort especially in young children. For that reason, it has been recommended for use in older children above the age of 4 years¹³. Despite its limitation, in health facilities where the equipment for monitoring full blood count is unavailable for making a diagnosis of dengue infection, particularly DHF, tourniquet testing repeated serially would be a useful diagnostic indicator by virtue of its high sensitivity. A positive reading alerts clinician to consider dengue infection as a current diagnosis in the patient and subsequent referral to a centre which can provide good observation and investigation facilities. Alternatively, parents might be taught to look for specific symptoms and asked to return daily to review signs.

The limitation of the study was the serological evidence of dengue infection was based on a positive dengue IgM ELISA. It is at least as specific and sensitive as the haemagglutination-inhibition test, the gold standard for dengue serological diagnostic test¹⁴. Although IgM ELISA produces positive results in acute specimens of secondary infections, dengue IgM may not appear until

the 7th day of illness in a primary infection. A second serum sample obtained prior to hospital discharge is required for definitive serodiagnosis; this could attribute to a false positive result. In other words, a child will demonstrate a positive tourniquet test in such a situation but with a negative dengue serology result.

In conclusion, it seems that in a hospital setting, the tourniquet test adds little to the diagnosis of dengue

infection/DHF. As illustrated in this study, it aids in the diagnosis of one-fifth of patients with DHF, who presents with a positive tourniquet test as the only bleeding manifestation. Used in a community, a positive tourniquet test, repeatedly performed, is a useful preliminary screening test in DHF as recommended by WHO. However, it is not very specific and has a high false positive rate.

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