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Research Article

Calculation of the Rate of Unaccountable Fluid Loss; an Indicator of Severity of Leaking Fluids from Blood Vessels

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Abstract: Leaking blood vessels is common to many disease conditions like dengue hemorrhagic fever, septicemia, eclampsia and nephrotic syndrome. Leaking blood vessels is the primary pathology in dengue hemorrhagic fever. Clinical evidence of leaking blood vessels includes body swelling, effusions, circulatory failure or rising hematocrit. However, these indicators are late indicators and signify only the result of leaking. This article presents the process of developing a formula to calculate the ongoing rate of fluid leak from a patient by using clinical parameters such as urine output, fluid intake and changes of the hematocrit (HCT). The formula to predict rate of fluid leak from blood vessels was developed on the basis that "the change of hematocrit over a defined period of time is the result of fluid intake, urine output, insensible loss, fluid leaking out of blood vessels and the fluid utilized for growth and metabolism". Out of these parameters fluid intake, urine output and changes in hematocrit could be measured. Other parameters like fluid for growth and metabolism and fluid that leak out cannot be measured. Therefore they are collectively termed as unaccountable fluid. Net rate of fluid leaking from blood vessels should be zero in health. Any amount of fluid leak should reflect pathology while the trends changing rate of fluid should reflect disease progress and severity. Therefore rate of fluid leak should help to assess efficacy of novel therapeutic interventions.
Theoretical basis of the development of the following formula is explained in this article.

$$\text{Rate of UFL ml per kg per hr } = \frac{80\ \left(1-\frac{PCV1}{PCV2}\right)}{T} + \frac{\text{V} - \text{U}}{W\ X\ T}$$

One way Analysis of Variance and hierarchical multiple regression analysis reveal that the calculated rate of unaccountable fluid loss correlates with the disease entity; dengue fever, dengue hemorrhagic fever and dengue shock syndrome and reflect the efficacy of dextran infusion. This formula could be used to monitor the rate of fluid leak during management of dengue hemorrhagic fever and other critically ill patients and for the evaluation of therapeutic interventions in these conditions.

Keywords: septicemia, eclampsia, nephrotic syndrome, hematocrit

INTRODUCTION

Many disease conditions are characterized by leakage of plasma from blood vessels into the extravascular compartment [1, 2]. Dengue hemorrhagic fever, septicemia, asphyxia, nephrotic syndrome and congestive heart failure are examples of diseases with leaking blood vessels.Recognition and evaluation of leaking blood vessels in these conditions depends on detection of body swelling, pleural or peritoneal effusions and circulatory failure.These indicators are late evidence of leaking blood vessels and probably not sensitive indicators of disease severity as they take some time to be clinically detectable.

Establishing the diagnosis of dengue hemorrhagic fever according to WHO 1997 case definition [3] or warning signs and severe dengue according to WHO 2009 case definition [4, 5] necessitates demonstrating evidence of leaking fluid from blood vessels as an essential criteria. Pleural or peritoneal effusions, developing circulatory failure and rising hematocrit (HCT) are considered as evidence of fluid leak in clinical practice [3-5]. Low albumin and low cholesterol also indicates leaking fluid. However, change in HCT, the most commonly used objective evidence of fluid leak in clinical practice is not without flaws. Twenty percent rise of HCT is considered as significant evidence of plasma leakage, which necessitates the knowledge of the baseline, HCT values. HCT is known to vary with age, sex, disease and level of hydration. Lower HCT values in anemic patients and higher HCT values in dehydrated patients complicate the

interpretation of HCT [3,4]. Similarly early fluid infusions will prevent rise in hematocrit despite leaking blood vessels. Therefore, a method of evaluating rate of fluid leak would be valuable in establishing the diagnosis, assessment of disease severity and gaging the rate of fluid infusions.

Dengue infections devastate populations as it engulfs the entire population with the fear of causing death. Recognition of severe form of the disease out of many mild forms of disease becomes very difficult. Therefore, researchers of western as well as native medicine propose many therapeutic interventions. Therefore, evaluation of efficacy of therapeutic interventions has become essential. Use of surrogate markers like number of deaths, ICU admission and fluid requirements are not specific and not sensitive. Therefore a method of evaluating the rate of fluid leak in diseases would be of great value.

In the present study, a hypothetical formula was developed for calculation of fluid leak and it was tested in a sample of dengue patients managed in a tertiary care center.

Rationale in developing the formula

Rate of Unaccountable Fluid Loss calculated by urine output, fluid intake and changes of HCT over a short period of time could assess the onset and severity of fluid leakage in diseases conditions characterized by plasma leakage like Dengue Hemorrhagic Fever.

Developing the mathematical formula

If we consider the amount of fluid given over a period of time (T hrs) as V ml, urine output as U ml and HCT at the beginning and end of observation as HCT1 and HCT2 respectively in a patient weighing W kg, a formula can be developed as follows. Insensible loss is considered as Y ml and the net fluid leak from blood vessels to the interstitial space is considered as X ml. Total blood volume at the beginning of observation is considered as BV1 and at the end of the observation is BV2

The relationship of total blood volume (BV), Total blood cell volume (TBCV) and the PCV can be expressed by the formula;

$$TBCV = BV * \frac{PCV}{100} \qquad \text{Equation 1}$$

Using above equation,

Total Blood Cell Volume at the beginning of the observation is

$$TBCV1 = BV1 * \frac{PCV1}{100} \qquad \text{Equation 1.1}$$

Total Blood Cell Volume at the end of the observation is

$$TBCV2 = BV2 * \frac{PCV2}{100} \qquad \text{Equation 1.2}$$

Total TBCV remains same over a short period of time if there is no acute bleeding. Therefore

TBV1 = TBV2

$$BV1 * \frac{PCV1}{100} = BV2 * \frac{PCV2}{100} \qquad \text{Equation 2}$$

$$BV2 = BV1 * \frac{PCV1}{PCV2}$$

Change in the blood volume (BV1 – BV2), which represents haemo-concentration, is the final result of plasma leak, production of urine and infusion of fluid and utilization of water for growth and losses due to evaporation.

If we assume that in an individual patient to whom a V volume of fluid has been given and U volume of urine has been passed, Y volume of fluid is lost as insensible loss and a Z volume of water has been used for growth following formula can be developed. Therefore total amount of fluid leaked out (L) can be expressed as follows.

$$L = V - (BV2 - BV1) + (U + Y + Z) \qquad \text{Equation 3}$$

Substituting Equation 2

$$L = V - \left\{BV1 * \frac{PCV1}{PCV2} - BV1\right\} - \{U + Y = Z\}$$

$$L + (U + Y + Z) = V - \{BV1(\frac{PCV1}{PCV2} - 1)\}$$ Equation 4

L, Y and Z together would be considered as unaccountable fluid.

Unaccountable fluid volume = $(L + Y + Z) = V - \left\{BV1\left(\frac{PCV1}{PCV2}\right) - 1\right\} - U$ Equation 5

BV1 can be estimated by assuming blood volume is equal to 80 ml/kg in a healthy child. If the weight of the child is W Kg;

BV1 = 0.8 x W

Final formula to calculate rate of unaccountable fluid loss over an observed period of time would be as follows.

Unaccountable fluid loss UFL $= (\mathrm{L} + \mathrm{Y} + \mathrm{Z}) = \mathrm{V} - \left\{80 * \mathrm{W}\left(1 - \frac{\mathrm{PCV\ 1}}{\mathrm{PCV\ 2}}\right)\right\} - \mathrm{U}$ Equation 6

Rate of Unaccountable Fluid Loss (RUFL) during the period of observation is UFL /W/T ml/kg/hr

RUFL; $(\mathrm{L} + \mathrm{Y} + \mathrm{Z})\ (ml/kg)/(hr) = (80\ W\ (1 - PCV1/PCV2))/(W\ X\ T) +\ (\mathrm{V} - \mathrm{U})/(W\ X\ T)$ Equation 7

$$\mathrm{RUFL}(ml/kg)/hr = \lfloor 80\ (1 - (PCV1/PCV2)\rfloor/\ T +\ (\mathrm{V} - \mathrm{U})/(W\ X\ T)$$ Equation 8

As L, Y and Z are not measurable, L+Y+Z is termed unaccountable fluid. Insensible loss is constant in a given environmental conditions and a constant physiological conditions of a patient. Fluid utilized for growth also will be constant over a short period of time. Therefore changes of the rate of unaccountable fluid loss will be a reliable indicator of fluid leak.

The above formula has been developed considering the blood volume as 80 ml /kg when the base line (HCTB) is normal. When patients present some time after the progression of the disease, their initial blood volume (BV1) can be calculated based on the HCT at the beginning of the observation. If the base line HCT is HCTB and HCT at the beginning of observation is HCT1 initial blood volume (BV1) would be calculated as follows.

$$\mathrm{BV1} = 80\mathrm{ml} * \frac{\mathrm{PCV\ 1}}{\mathrm{PCVB}}$$ Equation 9

This formula has been further developed as follows;

$$\mathrm{RUFL} = 80 * \mathrm{PCVB} * \left(\frac{\mathrm{PCV\ 2 - PCV\ 1}}{\mathrm{PCV\ 1 * PCV\ 2 * T}}\right) - \left(\frac{\mathrm{V - U}}{\mathrm{W * T}}\right)$$ Equation 10

In this final formula if the baseline PCVB is equal to the PCV1 final equation would be similar to

$$\text{RUFL ml/Kg/Hr} = \frac{80\left(\frac{1 - \mathrm{PCV\ 1}}{\mathrm{PCV\ 2}}\right)}{\mathrm{T}} + \frac{\mathrm{V - U}}{\mathrm{Wt/T}},$$ Equation 11

METHODS

The ethical review committees of the Faculty of Medicine, Paradeniya and Lady Ridgeway Hospital (LRH) approved this prospective observational study conducted over 8 months in LRH. All the patients observed after suspecting as DF/DHF/DSS observed in one of the unit in the LRH were recruited for the study. Case definition of DF/DHF/DSS was used according to national guidelines, which is similar to WHO 1997 guideline [3]. Routine monitoring charts used during management of patients were slightly modified in order to synchronize the timing of performing HCT and documenting fluid balance. Patients who were monitored with the suspicion of dengue but subsequently decided as viral fever were also incorporated in the study.

When the diagnosis of DHF with or without shock is suspected detailed monitoring of fluid intake, urine output, clinical parameters and HCT would be initiated as a part of the routine care. Experienced nurses perform in ward HCT

on venous blood using a capillary tube and a centrifuge as a routine practice. Frequency of performing HCT would be determined according to the clinically assessed disease severity; mild disease 4-6 hourly and more severe disease 1-2 hourly. Urine output is measured by a catheter in severely ill patients while patient with mild disease are asked void at the time of recording fluid balance. Fluid intake either IV or oral is recorded by the nursing officer, and parents are advised to measure whatever the fluid given to the child using the measuring syringe given to them. Type of fluid included oral fluid, normal saline, dextran or blood. At the time of obtaining the blood sample for HCT the nurse document the urine output and fluid intake during the observed time period from the previous HCT as an essential requirement of this study.

After the patient recovery or transfer to an ICU diagnosis was revised retrospectively. Some of the patient suspected of DHF were actually had dengue fever or viral fever. Some of the patients initially did not have shock-developed shock during the course of illness. All the data were entered to a programmed excel sheet and the rate of unaccountable fluid loss (ROUFL) at a specific times periods was calculated. ROUFL was correlated with age, sex, and disease severity, time from the onset of critical phase and whether dextran is given or not.

Data Analysis

The distribution of data was examined using histograms and Kolmogorov-Smirnov test. The maximum ROUFL of two patients were identified as outliers and eliminated from the analysis, this left 93 patients in the sample. Descriptive statistics were calculated for demographic data and maximum ROUFL. Floor and ceiling effect was examined using frequency distributions.

The ROUFL was compared between DF and DHF with and without shock using the one-way Analysis of Variance followed by Tukey post-hoc test.

The association of sex, age, weight and the diagnostic subgroup was explored using hierarchical multiple regression analysis. The blocks of variables entered were as follows: (a) sex and age, (b) weight and (c) diagnostic subgroup as DF and DHF with and without shock. The purpose was to isolate the effect of diagnostic subgroup on the ROUFL.

RESULTS

Monitoring charts of 93 patients were evaluated during the study period. Age and sex distribution of patients is given in the Table 1. Average calculated ROUFL according to the sex and the diagnosis is given in the Table 2. Mean (SD) maximum ROUFL among the patients with DF and DHF with and without shock were 3.3 (3.7), 10.7 (5.7) and 6.0 [3.4] respectively. One-way Analysis of Variance revealed that the differences among mean maximum ROUFL were statistically significant ($F=21.37$, $P<0.001$). Tukey post-hoc tests revealed that the means of three groups were significantly different from each other ($P<0.05$).

Hierarchical multiple regression analysis revealed that age ($P<0.05$), weight ($P<0.001$) and diagnosis contributed significantly to ROUFL (Table 4). Addition of diagnosis into the model gives rise to greatest F-Change ($P<0.001$) illustrating how powerful it is. A significant effect of sex was not observed. Comparison of the ROUFL in DF/VF, DHF without shock and DHF with shock according to the time from the onset of entry in to the critical phase of the illness is given in Figure 1. Trends of the ROUFL in DF/VF, DHF 1&2 and DHF 3&4 according to time from the onset of the critical phase are given in figure 2. Mean RULF when dextran was infused was – 7.4 (SD 8.6) as compared to 1.9 (SD 3.8) with saline infusion and were significantly different ($t=20.25$, $P=0.001$).

Table-1: Age and sex distribution of the patients included in the study

Age	Total	Male	Female
Less than 4 years	12	8 (67%)	4 (33%)
4- 7 years	22	11 (50%)	11 (50%)
7- 10 year s	31	14 (45%)	17 (55%)
Above 10 years	28	15(54%)	13 (46%)
Total number	93	48 (51.6%)	45(48%)

Table-2: Average maximum rate of unaccountable fluid loss (ROUFL) according to the sex and diagnosis

Sex	DF or VF	DHF without shock	DHF with shock
Male	2.3 (0.77)	7.04 (3.7)	11.4 (6.63)
Feale	4.05 (4.82)	4.7 (2.7)	9.6 (4.1)

Table-3- Comparison of maximum rate of unaccountable fluid loss with duration in the critical phase among three categories of patients

Hours in the critical phase	Less than 12 hours			12- 24 hours			24-36 hours			More than 36 hours		
Diagnosis group*	1	2	3	1	2	3	1	2	3	1	2	3
Number of readings	99	148	57	59	134	68	60	108	119	74	109	179
Maximum Rate of Unaccountable Fluid Loss	0.34	1.78	3.74	0.50	2.14	3.34	0.61	1.71	3.53	0.20	1.96	2.63
SD	4.33	2.60	4.01	1.80	3.68	4.60	2.08	2.46	3.94	1.56	3.08	5.65

*Diagnosis group 1 – Viral fever and dengue fever, 2 – Dengue Haemorrhagic Fever without shock 3 – Dengue Haemorrhagic Fever with shock

Table 4 – Comparison of ROUFL before and after infusion of dextran among patient with DHF with shock (n=34)

	When dextran is not infusion	During dextran infusion
Number of observations	567	73
RUFL	2.89	-9.71

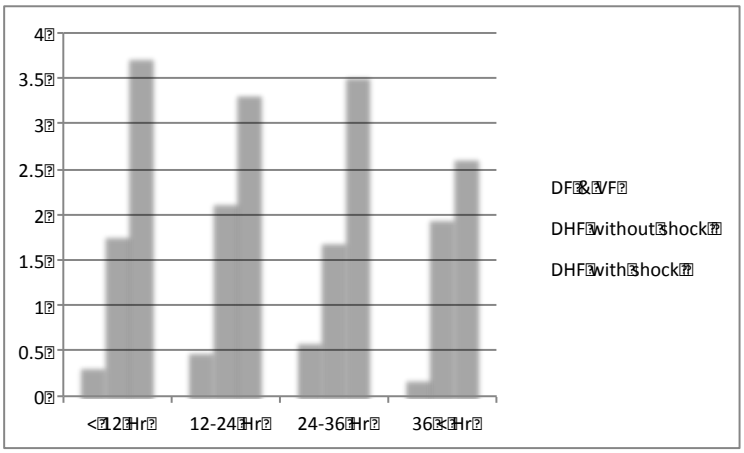

Fig-1: Comparison of the ROUFL in DF/VF, DHF without shock and DHF with shock according to the time from the onset of entry in to the critical phase of the illness

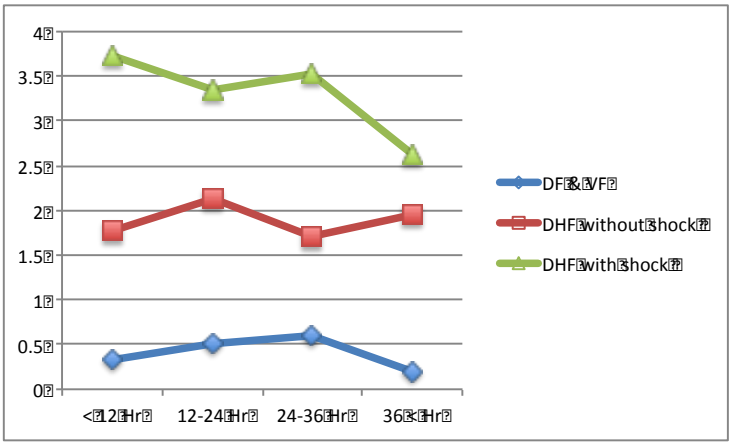

Fig-2: Trends of the ROUFL in DF/VF, DHF without shock and DHF with shock according to time from the onset of the critical phase

Table-5: Hierarchical regression analysis for predictors of ROUF

Predictors and Blocks	Model for RPR for DH	
	β	t
Block 1	$R^{2=}$0.06, F=3.05*, ΔR^2=0.5, ΔF=3.06 *	
Sex	-0.13	-1.27
Age	-0.21	-2.06 *
Block 2	$R^{2=}$0.13, F=4.3**, ΔR^2=0.06, ΔF= 6.3 *	
Sex	-0.12	-1.13
Age	0.05	0.34
Weight	-0.36	-2.52*
Block 3	$R^{2=}$0.4, F=14.1***, ΔR^2=0.3, ΔF=38.3***	
Sex	-0.05	-0.57
Age	0.05	0.38
Weight	-0.31	-2.51*
Diagnosis	0.52	6.18***

β Coefficients, t values and the significance levels are given for each predictor under every block.
ΔR^2, R^2 change. * *P< .05;* ** *P< .01;* *** *P< .001.*

DISCUSSION

Dengue is endemic in tropics and subtropics, where 40% of the world population is living. Seasonal epidemic are a constant feature due to the life cycle of the transmitting vector *Aedesaegypti* and *Ae. albopictus* mosquitoes. Out of 400 million people infected by any of four-dengue viruses (DENV1, 2, 3, and 4) worldwide, 100 million develop symptomatic illness [5] majorities are asymptomatic or have non-specific febrile illness, while others develop classical dengue fever with or without bleeding manifestations. Patients with dengue develop nausea/vomiting, rash, aches and pains (headache, retro orbital pain, joint pain, and muscle pain), tourniquet test positive, leucopenia (WBC < 5000/mm^3) and platelet count less than 150 000/mm^3. Out of those who are symptomatic only 0.5 million cases develop dengue hemorrhagic fever that carry some degree of mortality and morbidity [6]. Only 5% of the infected people will develop severe illness which is an illness characterized by plasma leakage leading to hypovolemic shock and hemorrhage with a case fatality rate of 10% if untreated, or 0.1% with appropriate clinical management [5]. The causes of increased vascular permeability are attributed to disruption of tight junctions of the human vascular endothelial cells dependent on internally produced mediators [7,8].

Evidence of fluid leaking from blood vessels plays a major role in case definition of DF/DHF/DSS WHO 1997 [4] or recognizing dengue fever with warning signs and severe dengue WHO 2009 [5,6]. Recognition of dengue with warning signs and severe dengue [4] has advantages of been able to classify almost all cases evaluated except for 1.6% of cases, while DF/DHF/DSS classification has failed to classify 14% of the cases and 22% of dengue with shock has not fulfilled criteria for DHF [9]. However this study followed the DF/DHF/DSS classification according to the national guideline for management of dengue in the health care system of the country.

Dengue hemorrhagic fever develops over three phases; febrile phase, critical phase and recovery phase. During the febrile phase the child has high fever, body pain, skin rashes and many other non-specific symptoms. They are flushed and those who develop dengue hemorrhagic fever are likely to develop tender hepatomegaly at this stage. White cell count typically shows a picture of viral infection. Total white cell count and platelet count tend to decline gradually. Dropping platelet counts below 100,000/dl is considered as the time of the onset of leaking blood vessels or the critical phase. Total white cell count drops below 5000/dl 24 hour prior to the onset of leaking. However actual fluid leaking could only be recognized when the HCT start rising. Fluid leaking tends to progress over 24 hours coming to a peak and start declining over next 24-48 hours. Rate of fluid leak and the disease severity in DHF vary; some manage to compensate and develop non-shock DHF. Non-shock DHF without any bleeding is DHF grade one and with evidence of bleeding they are categorized as DHF grade 2. Minority of patients have severe leaking leading to shock; those develop severe shock with no palpable pulse are categorize as DHF grade 4 and other are categorized as grade 3 [3-5].

The ROUFL seems to correlate with the clinical diagnosis. Patients with viral fever and dengue fever have lowest ROUFL.Highest ROUFL is seen among patients with DHF with shock. DHF without shock was placed in between. Similarly as the natural history of the disease suggests ROUFL is progressing over the first 24 hours and decline to a minimal level towards the end of the 48 hours. However ROUFL remains high in the DHF group than DF/VF group. ROUFL become negative after infusion of dextran. This is an objective evidence of fluid influx after dextran infusion. Therefore ROUFL seems to reflect the pathological process in dengue.

Management of dengue hemorrhagic fever is entirely based on judicial administration of fluid to ensure the provision of just sufficient amount of fluid to maintain the circulation. Provision of too much of fluid or hypotonic fluids can lead to fluid overload and their complications, while provision of inadequate volumes of fluid can lead to circulatory failure and shock. In clinical practice, rising HCT, urine output and the clinical picture of the patient will support to determine rate of infusion of fluid.

Calculating the rate of unaccountable fluid loss will provide a useful guide for determining the onset and the progress of the disease. ROUFL could be calculated at a selected period of time creating an opportunity to test the impact of any therapeutic intervention. This study has demonstrated negative value after infusion of dextran indicating validity of the formula.

CONCLUSIONS

The ROUFL can easily be calculated using three simple measurable values; HCT, fluid input and urine output in clinical practice.This index that appears to correlate with the rates of fluid leaking will be a valuable tool in evaluating diseases with leaking blood vessels like DHF/sepsis for research and management of such patients.The ROUFL appears toreflect the stage and the severity of leaking. Sensitivity and specificity of ROUFL should be studied further as an indicator of the rate of leaking.

The ROUFL seems to reflect the stage and severity of leaking over a specific period of time in DHF. The negative ROUFL indicate fluid influx during dextran infusion. ROUFL is an indicator of disease severity that could be utilized in research to evaluate any patient with leaking blood vessels.Correlation of ROUFL with warning signs and severe dengue (WHO 2009 classification) would be valuable future research topic.

Limitations

- Formula used to estimate blood volume may not be universally similar between different age groups and children with different BMI values as we assume that the total blood volume is 80ml/kg.
- Insensible loss of fluid was considered as constant. However it can change with environmental conditions as well as patient's conditions like temperature, hydration and clothing. Therefore comparison of values of ROUFL in single patients may be slightly influenced
- Total blood cell volume was considered as constant during the period of observation. However if there is bleeding this assumption is not valid. Clinician should be aware of this fact. Similarly rapid production of cells may change the total cell volume in a given patient in a short time.

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