Calculation of the Residual Blood Volume after Acute, Non-Ongoing Hemorrhage Using Serial Hematocrit Measurements and the Volume of Isotonic Fluid Infused: Theoretical Hypothesis Generating Study

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Fluid resuscitation, hemostasis, and transfusion is essential in care of hemorrhagic shock. Although estimation of the residual blood volume is crucial, the standard measuring methods are impractical or unsafe. Vital signs, central venous or pulmonary artery pressures are inaccurate. We hypothesized that the residual blood volume for acute, non-ongoing hemorrhage was calculable using serial hematocrit measurements and the volume of isotonic solution infused. Blood volume is the sum of volumes of red blood cells and plasma. For acute, non-ongoing hemorrhage, red blood cell volume would not change. A certain portion of the isotonic fluid would increase plasma volume. Mathematically, we suggest that the residual blood volume after acute, non-ongoing hemorrhage might be calculated as $0.25N/[(Hct_1/Hct_2)-1]$, where Hct_1 and Hct_2 are the initial and subsequent hematocrits, respectively, and N is the volume of isotonic solution infused. In vivo validation and modification is needed before clinical application of this model.

Keywords: Blood Volume Determination; Hematocrit; Isotonic Solutions; Hemorrhagic Shock; Traumatic Shock

Trauma causes 5 million deaths annually (10% of all-cause mortality), and is the most common cause of death (40%) in those aged 10-24 years (1,2). Hemorrhagic shock is the foremost cause of traumatic deaths, and is the main target of resuscitation, especially in the early management stages (3,4). Furthermore, hemorrhagic shock occurs in numerous non-traumatic patients, and optimal treatment is likewise critical in these patients (5).

The cornerstone in the initial management of patients with hemorrhagic shock is damage control resuscitation, characterized by cautious isotonic fluid resuscitation (permissive hypotension) and hemostatic resuscitation with an adequate transfusion strategy until definitive control of hemorrhage (6-8). Therefore, the residual blood volume (BV) in hemorrhagic patients at the time of first contact with medical personnel is a reasonable parameter to guide the initial management. In contrast to the management of chronic anemia, however, hematocrit (Hct, %) measurements cannot represent the BV in patients with acute hemorrhagic shock (9,10). The Hct, defined as the red blood cell volume (RBCV) divided by the BV [= RBCV + plasma volume (PV)], remains unchanged in hyperacute bleeding, and the Hct is not decreased until the PV is increased by shifting the interstitial fluid from the surrounding tissue.

Clinicians usually estimate BV loss according to the guidelines of the American College of Surgeons. Using vital signs, urine output, and mental status, the BV loss is categorized as class I-IV (< 15, 15–30, 30–40, > 40% of the total BV, respectively) (7). However, this method is semi-quantitative and less applicable in the management of patients who take negative chronotropes such as beta- or calcium channel blockers, which impede compensatory tachycardia, one of the key parameters of the classification. Furthermore, this classification system falls short in management of the elderly and children (7). Central venous and pulmonary artery occlusion pressures are quantitative, but cannot accurately reflect the BV (11,12). The reference standards to measure the residual BV using radioisotope-labeled erythrocytes, albumin, indocyanine green, or starch are impractical in the earliest management of hemorrhagic shock due to their complexity and the potential for harm to these patients (13,14). Recently, dynamic indicators to reflect volume responsiveness have been introduced, including the stroke volume variation, pulse pressure variation, systolic pressure variation, and the passive leg raising test (15). However, these methods require specialized equipment and the results are semi-quantitative.

Given that clinicians generally perform subsequent Hct measurements after infusion of certain amounts of isotonic solutions during the initial management of patients with hemorrhagic shock, we hypothesized that the Hct values and isotonic

Timing	RBCV	PV	BV $(= RBCV + PV)$	Hct $(= RBCV/BV)$
① Initial contact with medical personnel	$RBCV_1$	PV_1	BV_1 $(= RBCV_1 + PV_1)$	Hct_1
Initial resuscitation with isotonic solution of N (mL) (k: the fraction of isotonic solution added to PV,			would add $k*N$ (mL) to PV without changing RBCV. with the remnant (1-k) fraction to interstitial fluid)	
② Checking subsequent Hct (Hct_2) after infusion of N (mL) of isotonic solution	$RBCV_2 = RBCV_1$ (unchanged)	$PV_2 = PV_1 + k*N$	$BV_2 = RBCV_2 + PV_2$ $= RBCV_1 + (PV_1 + k*N)$ $= (RBCV_1 + PV_1) + k*N$ $= BV_1 + k*N$	Hct_2

Fig. 1. The change in red blood cell volume (RBCV), plasma volume (PV), blood volume (BV), and hematocrit (Hct) according to time after acute, non-ongoing hemorrhage.

solution infusion volume could be used to calculate the residual BV after acute, non-ongoing hemorrhage.

When patients with hemorrhagic shock present to the emergency department (Stage 1: the time of initial contact with medical personnel), the standard management consists of obtaining blood samples including the initial Hct, rapid infusion of 30 mL/kg of isotonic solutions (usually normal saline) before possible transfusion, and immediate hemostasis as soon as possible. Usually, clinicians check subsequent Hct values (Stage 2: the time to check subsequent Hct), while loading the isotonic solution. Using the designation of subscript of 1 and 2, we can define the BV, PV, and Hct at each time point as described in Fig. 1.

Conceptually, the isotonic solution is distributed to the extracellular fluid compartments, which comprise the interstitial fluid compartment and the PV, without entering the intracellular compartments. This distribution of the resuscitation fluid occurs mostly within the first 30 minutes, which would be usually needed for the initial fluid resuscitation in practice from stage 1 to stage 2 (16). If the fraction of isotonic solution distribution into the PV is k (where $0 < k < 1$), infusion of N (mL) of isotonic solution will add $k*N$ to the PV. Then,

$PV_2 = PV_1 + k*N$ … ①

For a non-ongoing hemorrhage, the RBCV remains unchanged.

$RBCV_1 = RBCV_2$ … ②

Therefore,

$BV_2 = RBCV_2 + PV_2$ [by definition of BV]
$= RBCV_1 + (PV_1 + k*N)$ [by incorporating ① and ②]
$= (RBCV_1 + PV_1) + k*N$
$= BV_1 + k*N$ … ③ [by definition of BV]

Meanwhile,

$RBCV_1 = BV_1*Hct_1$ … ④ [by definition]
$RBCV_2 = BV_2*Hct_2$ [by definition]
$= (BV_1 + k*N)*Hct_2$ … ⑤ [by incorporating ③]

If we incorporate ④ and ⑤ into ②, which assumes non-sustained hemorrhage, then

$BV_1*Hct_1 = (BV_1 + k*N)*Hct_2$ [by incorporating ④ and ⑤]

Then, BV_1, the ultimate target of our study can be demonstrated as follows:

$BV_1 = (k*N)/[(Hct_1/Hct_2)-1]$

Among the components of the equation, N (mL) is the infused isotonic solution volume, determined by the clinician, and the Hct_1 and Hct_2 values are serial measurements.

Additionally, k represents the fraction of the isotonic solution distributed into the PV, which differs among species. If k were to be presumed as 0·25 in human (17), BV_1 might be restated more simply as follows:

$BV_1 = 0·25N/[(Hct_1/Hct_2)-1]$ (mL)

To simplify the formula for easy use by clinicians, N could be predetermined as 1,000 or 2,000 mL. Then BV_1 (mL) might be calculated as follows: $250/[(Hct_1/Hct_2)-1]$ (in cases with $N = 1,000$ mL) and $500/[(Hct_1/Hct_2)-1]$ (in cases with $N = 2,000$ mL) on the condition that following studies support that k is 0·25 even in patients suffering from acute, non-ongoing hemorrhage.

This study demonstrated that the residual BV after controlling acute hemorrhagic events could be calculated in patients using serial hematocrits and the volume of the isotonic solution infused, by employing the following equation: $k*N/[(Hct_1/Hct_2)-1]$, where k is the fraction of isotonic solution distribution into the PV, N is the volume of isotonic solution infused between the two hematocrit measurement time points, and Hct_1 and Hct_2 are the initial and subsequent hematocrits, respectively.

This equation has several merits. Firstly, this simple equation may provide a quantitative measurement of the residual BV, which would guide further intensive management of patients after acute, non-ongoing hemorrhage. Secondly, it utilizes no more resources and does no more harm other than those needed for conventional management, unlike other invasive, expensive, semi-quantitative, or potentially harmful methods (11-15,18).

This hypothesis-generating study has several limitations. Firstly, this model has been derived mathematically with following assumptions, which may not apply to clinical situations. According to the traditional perspectives, the authors assumed that fluid shift to intravascular compartment after acute hemorrhage would take much time (7,9,10). However, some investigators raised the possibility that this shift might occur faster than ex-

pected, which may alter the assumption, although more evidences are needed to support their opinion (19). We neither considered the factors, which may influence the model, such as the integrity of the vasculature, severity of hemorrhage, and renal output although the last would be negligible in hemorrhagic shock (16,20). All of the limitations arising from the mathematical assumptions without these clinical considerations will ultimately alter the k, which we assumed to be 0·25. That is one of the very reasons that we need to validate and modify this model (esp. k) at varying degrees of hemorrhage in vivo before it could be applied to clinical situations.

Another limitation of our model is that it is applicable only to non-ongoing hemorrhage as we assumed so. Although non-ongoing hemorrhage may not result in mortality, the estimation of the residual volume would be still valuable in that clinicians may decide the minimum requisite volume of blood product by this estimation, which will help lowering the risk of transfusion. When the ongoing blood loss is large enough, a more complicated model would be required. To build up this complex model, the model suggested by this study might provide the theoretical basis.

In summary, we suggest that the residual BV after acute, non-ongoing hemorrhagic shock might be calculated theoretically using $0·25N/[(\text{Hct}_1/\text{Hct}_2)-1]$, where Hct_1 and Hct_2 are the initial and subsequent hematocrits, respectively, and N is the volume of isotonic solution infused between these time points. This model needs in vivo validation and modification with successive studies in order to guide the practical management of acute, non-ongoing hemorrhage by estimation of the residual blood volume.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception of the theoretical hypothesis: Chon SB. Manuscript preparation, revision, and approval: all authors.

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