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Computer simulation of transfusion with different blood product ratios in modern massive transfusion protocols

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ABSTRACT

Modern massive transfusion protocols call for early plasma and platelets to patients presenting with hemorrhagic shock. The packed red blood cell (PRBC):plasma:platelet ratio generally ranges from 1:1:1 to 3:1:1, but the ideal ratio remains controversial. We aimed to determine the effects of different resuscitation strategies and blood product ratios on hematocrit, platelet and fibrinogen concentrations (FC) during resuscitation. Assuming: pre-insult blood volume 5 L; hematocrit 0.4, FC = 100%, platelet count 400 × 10^9/L; predetermined constant values for each blood product unit (volume, hematocrit, FC, platelet number); and transfusion rate to maintain euvolemia, we simulated different resuscitation strategies using a computer-based hemorrhage model. When crystalloids are administered to restore an acute 30% blood loss, the initial hematocrit, platelets and FC are adequate, and remain physiologic when further resuscitation is carried out with 1:1:1. Higher transfusion ratios increase the hematocrit at the expense of proportional drops in FC and platelets. When crystalloids and PRBCs (1500 mL) are administered to restore an acute 60% blood loss, the FC drops to 39%. Further resuscitation with 1:1:1 (but not with 2:1:1 or 3:1:1) increases the FC while maintaining the hematocrit and platelets within physiologic range. When blood products (1–3:1:1) are administered to restore an acute 60% blood loss, the initial hematocrit, platelets and FC are at adequate levels, but remain within physiologic range only when 1:1:1 (but not 2:1:1 or 3:1:1) is implemented for further resuscitation. Notably, platelet concentration consistently drops in all simulated scenarios reaching dangerously low levels particularly with high blood loss/transfusion rates and with higher transfusion ratios. The FC does not always drop by the same proportion with higher ratios probably because it is based on plasma concentration and is thus "cushioned" by the reduction in plasma volume as the hematocrit rises with higher transfusion ratios. In summary, computer simulation suggests that in non-severe shock hemorrhage, the differences between 1-3:1:1 transfusion ratios during initial resuscitation may be small. In severe shock, however, 1:1:1 results in the most physiologic hematocrit, FC and platelet concentration and is, therefore, desirable.

Introduction

Massive transfusion in trauma has changed over the years from withholding fresh frozen plasma until one blood volume has been lost, and test results and/or clinical observation indicating severe coagulopathy is present to more proactive use of plasma, platelets, and fibrinogen [1]. Most U.S. trauma centers now have massive transfusion protocols (MTPs) that call for early availability of plasma and platelets (and sometimes fibrinogen) at a certain packed red blood cell (PRBC):plasma:platelet ratio to select patients presenting with hemorrhagic shock [2,3]. This ratio ranges from 1:1:1 to 3:1:1 or, rarely, higher [1–3]. A patient who has suffered substantial blood loss is often resuscitated initially with crystalloid and PRBCs. If hemorrhage continues, one or more batches of PRBCs, plasma, and platelets is made available immediately. If pre-thawed plasma is available and the shock is severe, resuscitation may begin immediately with PRBCs, plasma, platelets, and sometimes fibrinogen. This "shotgun approach" restores intravascular volume and minimizes coagulopathy during the early phase of resuscitation. It is modified when test results become available and a clearer clinical picture emerges [4]. Within this paradigm, the best *starting* ratio is a matter of much debate. Retrospective studies suggest a ratio 1–2:1:1 is better than > 2:1:1 [5]. One study found 2:1:1 to be better than 1:1:1 [6], while another found no difference within the range of 1–3:1:1 [7]. In a randomized controlled trial, 1:1:1 resulted in greater proportion of hemostasis and lower mortality due to exsanguination at 24 h than 2:1:1, but no significant difference was observed in overall 24-hour and 30-day mortalities [8]. This uncertainty has resulted in variable ratios ranging from 1:1:1 to 3:1:1 being

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Table 1
Simulated scenarios. PRBC = packed red blood cell unit.

Initial blood loss	1.5 L (30% of total blood volume)								3 L (60% of total blood volume)																
Euvolemia initially restored with	Crystalloid								PRBC 1.5L (5 units) and crystalloid								All blood products from the start in 1:1:1, 2:1:1 or 3:1:1 ratio								
Ongoing loss (mL/min)	25			50			75		25			50			75		25			50			75		
PRBC:plasma:platelet*	3:1:1	2:1:1	1:1:1	3:1:1	2:1:1	1:1:1	3:1:1	2:1:1	1:1:1	3:1:1	2:1:1	1:1:1	3:1:1	2:1:1	1:1:1	3:1:1	3:1:1	2:1:1	1:1:1	3:1:1	2:1:1	1:1:1	3:1:1	2:1:1	1:1:1
Scenario	1a	1b	1c	2a	2b	2c	3a	3b	3c	4a	4b	4c	5a	5b	5c	6a	6b	6c	7a	7b	7c	8a	8b	8c	9a	9b	9c

* Blood product ratios to replace ongoing blood loss after initial resuscitation.

used in different centers [1,3,9]. The general consensus in the UK is a ratio of 1–2:1:1 [10].

When there is a dearth of experimental data or when data are conflicting, simulation may shed light on the approximate behavior of a medical intervention. Most clinicians are familiar with simulations that replicate real-world events (e.g., mock cardiorespiratory arrest, trauma resuscitation). Biologists may mathematically simulate growth patterns of cancer cells, cardiovascular and pulmonary physiology under different conditions, or the effects of clotting factor deficiencies, hypothermia, or acidosis on clotting times. In public health, simulation is used to determine the cost effectiveness of preventative measures (e.g., vaccination, herd immunity). In the present study, simulation is used to calculate the theoretical concentrations of hemoglobin, fibrinogen, and platelets in different hemorrhagic and transfusion scenarios.

The causes of trauma coagulopathy include activation of protein C, acidosis, consumption, hypothermia, and dilution [11]. Dilution, in particular, may contribute to coagulopathy in major surgical blood loss. Hiippala et al assessed the dilution of hemostatic factors in elective surgeries when blood loss (65% ± 41% of blood volume) was concurrently replaced with PRBCs and colloids to maintain euvolemia, and estimated that the amount of bleeding required for fibrinogen, platelets, prothrombin, and factors V and VII to reach critical hemostatic levels was 142% (95%CI 117–169%), 230% (169–294%), 201% (160–244%), 229% (167–300%), and 236% (168–277%), respectively, of the blood volume [12]. Murray et al found in scoliosis repair that dilutional coagulopathy results when major blood loss was replaced with PRBC and crystalloids, and increased surgical bleeding was reversed with plasma administration [13]. Hiippala et al and Murray et al's results, which are based on the old practice of initially withholding plasma, remain relevant in today's practice of more proactive plasma and fibrinogen administration in the trauma setting. Importantly, dilution is arguably the only totally preventable cause of coagulopathy in trauma. The purpose of our simulation is to calculate the effect of dilution based on the modern MTP in trauma resuscitation, and to contribute to the debate on the "best" blood product ratio(s) under different conditions.

Methods

We chose fibrinogen as our prototype because of its critical role in hemostasis, it is the first factor to fall to critical levels during hemorrhage [12–14], and the fact that the amount of fibrinogen administered in trauma is positively correlated with survival [14]. Furthermore, its intravascular half-life of > 4 days [15] allows us to ignore the effect of transcapillary efflux and reflux and clearance in a 3-h simulation timeframe. Our model assumes the following conditions: pre-insult hematocrit 0.4, plasma fibrinogen concentration (FC) 100%, platelet count 400 × 10^9/L (this high-normal platelet concentration was chosen to account for the acute phase increase seen during the stress response to trauma); each PRBC unit contains 300 mL (hematocrit 75%); each donated plasma unit is 250 mL (FC = 100%); each platelet unit is 50 mL (6 × 10^{10} platelets); blood products are administered in sequence rather than all PRBCs, followed by all plasma, and so on.

The simulation begins at time 0 at which the initial blood loss (1.5 or 3 L) has been acutely replaced and euvolemia restored, and stops at the 180-min mark.

We used a spreadsheet program (EXCEL, Microsoft, Redmond, WA, USA) to calculate the hematocrit, FC and platelet concentration at every min of the 0–180 min period during which a "patient" loses blood at certain rates and receives blood products in different fixed ratios. A 70-kg-"patient" (total blood volume 5 L) has acutely lost 1.5 L (moderate shock – scenarios 1–3) or 3 L (severe shock – scenarios 4–9) of blood. Through transcapillary refill and crystalloid/blood product administration, intravascular volume has been rapidly restored (time 0). As hemorrhage continues at different simulated rates (25, 50, and 75 mL/min, translating to 1.5, 3, and 4.5 L/hour), blood products in different ratios are given (Table 1) to maintain euvolemia.

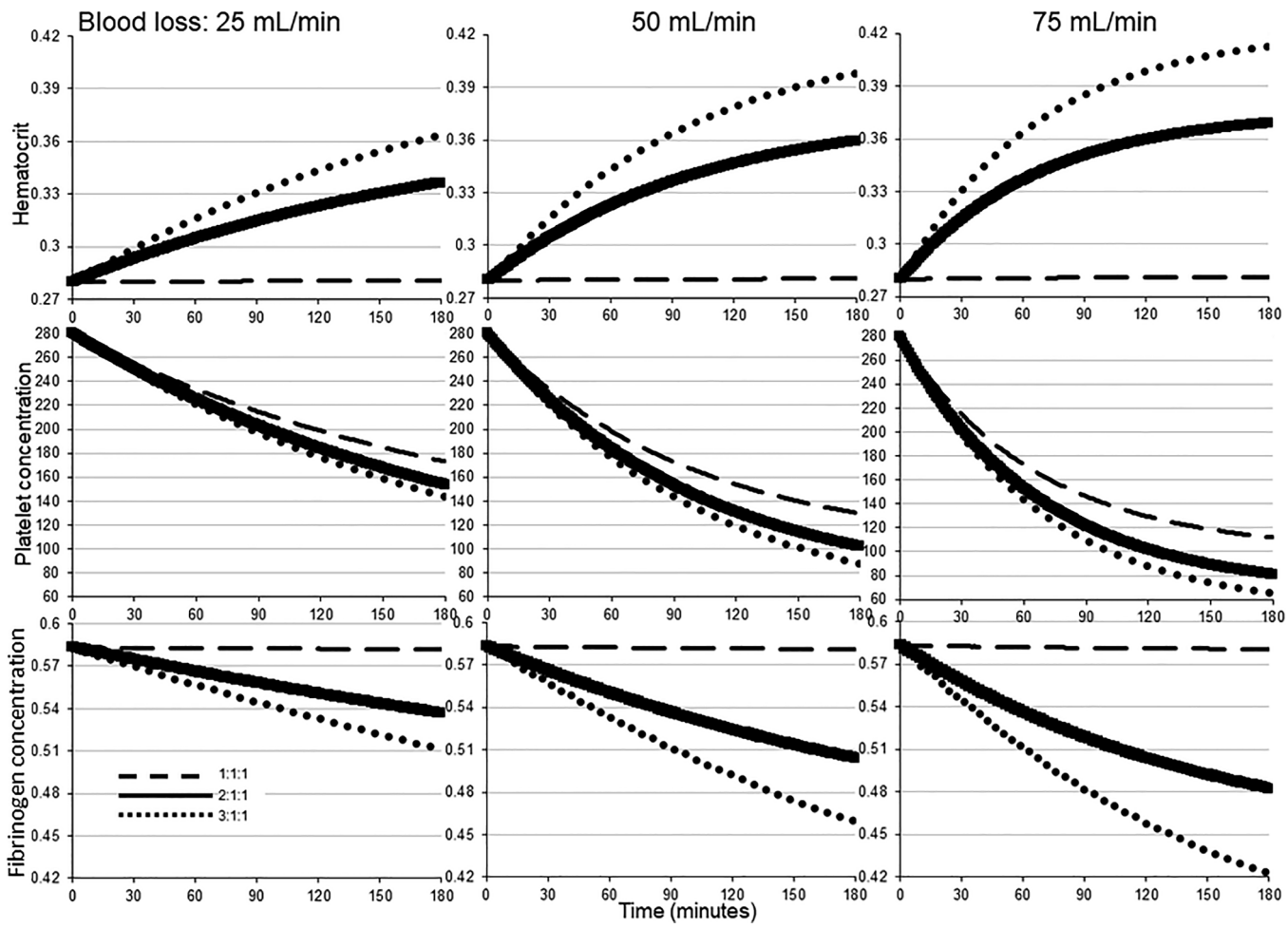

Fig. 1. Scenario 1–3. Initial blood loss 1.5 L; by time 0, intravascular volume has been restored with crystalloid. From time 0, hemorrhage and transfusion with PRBC:plasma:platelet ratio of 1:1:1, 2:1:1, and 3:1:1 at 25, 50, and 75 mL/min.

Results

Fig. 1 (Scenarios 1–3), 2 (Scenarios 4–6), and 3 (Scenarios 7–9) show how the hematocrit, FC, and platelet concentration change with time during resuscitation. Readers should take note of the use of different scales in the figures.

Scenarios 1–3: After intravascular volume is restored with crystalloid after an acute loss of 30% of total blood volume, the initial hematocrit (~28%), platelet concentration (~280×10^9/L) and FC (~58%) are at adequate levels (assuming no major coagulopathy caused by consumption, acidosis, or hypothermia). As expected, with 1:1:1 the hematocrit and FC stay relatively unchanged while the platelet count drops but remains within physiologic levels irrespective of the blood loss/transfusion rate. With higher transfusion ratios, the hematocrit rises at the expense of drops in FC and platelets, which are proportional to the blood loss/transfusion rate. Notably, the decrease in platelets was more pronounced especially with higher rates of blood loss.

Scenarios 4–6: After intravascular volume is restored with 5 units of PRBCs plus crystalloid after an acute loss of 60% of total blood volume, the initial hematocrit (~38%) and platelet concentration (~160×10^9/L) are physiologic but FC starts at 39%, which is a marginally acceptable level assuming the absence of other causes of coagulopathy. With 1:1:1, FC increases while hematocrit and platelet concentration decrease, but still remain within acceptable/physiologic range. With higher transfusion ratios, the hematocrit remains nearly unchanged (2:1:1) or increases (3:1:1), with more pronounced drops in platelets and a modest increase (2:1:1) or further drop (3:1:1) in FC. The trends are exaggerated with faster blood loss and transfusion.

Scenarios 7–9: After intravascular volume is restored with blood products of various ratios after an acute loss of 60% of total blood volume, the initial hematocrit, platelet concentration and FC are at adequate levels, except for an excessive hematocrit (~50%) with 3:1:1. With 1:1:1, all levels remain within physiologic range regardless of the blood loss/transfusion rate. At the higher transfusion ratios thrombocytopenia soon develops although the level of FC dilution is not serious enough to drop the concentration below 45%.

Discussion

No incidence of the hematocrit dropping below unacceptable level is found in our scenarios. In fact, a supranormal hematocrit (~50%) of questionable benefit occurs when one starts the MTP incorporating a 3:1:1 ratio as soon as shock is presented and volume infusion starts. Starting with a high transfusion ratio mimics initial transfusion with O-negative PRBCs while waiting for blood results or plasma to be thawed.

In contrast, the hemostatic blood components do not fare well with a high transfusion ratio in some situations. Despite an initially high-normal platelet count (400×10^9/L) before hemorrhage starts, platelet concentration drops to dangerously low levels particularly with high blood loss/transfusion rates and with higher transfusion ratios. The FC does not always drop by the same proportion with higher ratios probably because it is based on plasma concentration and is thus "cushioned" by the reduction in plasma volume as the hematocrit rises with higher ratios. This mitigating effect is probably clinically relevant and acceptable as long as the hematocrit remains in the physiologic range. Platelet concentration is based on total blood volume and therefore its

drop is not mitigated by reduction in plasma volume.

In moderate shock (Fig. 1), the differences in hematocrit, FC and platelet concentration between the different ratios (1–3:1:1) are relatively small (though more pronounced as blood loss/transfusion rate increases), and, depending on whether there are other causes of coagulopathy, may not necessarily be of major clinical relevance. In a dynamic setting of trauma where hypothermia, acidosis and consumption coagulopathy are almost invariably present, however, 1:1:1 represents the most physiologic resuscitative approach during ongoing hemorrhage, especially with high rates of blood loss/transfusion.

In severe shock (initial loss of 60% of total blood volume), patients may initially be resuscitated with a combination of crystalloid and several units of PRBCs, followed by a more balanced blood product transfusion (Fig. 2). Our simulation shows that while the hematocrit starts off adequate after this initial PRBC plus crystalloid infusion, the FC is already far from optimal. This inadequacy worsens as bleeding and transfusion continue and a 3:1:1 ratio is used. Even if a 1:1:1 ratio is used, the improvement is extremely slow, barely reaching 54% after 3 h of resuscitation with a high rate of bleeding and transfusion.

When thawed plasma is available, resuscitation with all blood products may start immediately in the presence of severe shock (Fig. 3). Starting massive transfusion with a 3:1:1 results in unnecessarily high hematocrit (~50%). In comparison, starting with 1:1:1 in severe shock results in the most physiologic hematocrit, FC and platelet concentration.

The best blood product ratio, if there was one, for exsanguinating trauma is unknown. Most observational studies suggest that a PRBC:plasma:platelet ratio of 1–2:1:1 is associated with increased survival when compared to > 2:1:1. Teixeira et al found no difference between 3:1:1 and lower ratios, but higher ratios resulted in decreased survival [7]. Kashuk et al determined that a 2:1 PRBC:plasma ratio had better survival than 1:1 [6]. Many of these retrospective analyses were prone to survivorship bias [16].

Experimental trials offer robust data but are difficult to perform. In a randomized study comparing blood ratios, less hemorrhagic death occurred in the group given 1:1:1 than in the group given 2:1:1, but no significant mortality difference was found after 24 h and 30-days (which might have been confounded by the effect of delayed death after head injury [8]). There were also no differences in 23 pre-specified complications. Not surprisingly, there are flaws in the execution of such a complex trial [17] and the ideal initial blood product ratio remains controversial.

Our simulation suggests that within 1–3:1:1, the differences in hemostasis in non-severe shock may be small. Consistent with our results are data from Galganski et al's study on transfusion in massive burn excision in children, which showed no difference in Protein C, fibrinogen, and hemoglobin during transfusion between PRBC:plasma ratios of 4:1 and 1:1. The mean INR in the 4:1 and 1:1 groups was 1.3 and 1.19 at the 1-hr mark, respectively, and the corresponding mean aPTT was 39 and 33 sec. By 12 h, these significant differences had resolved [18]. In an *in vitro* study, the mean FC for a 3:1:1 mixture was 60% compared with 82% for a 1:1:1 mixture. The resultant mean INR was 1.2 and 1, respectively [19].

Simulation is widely used in the sciences and in medicine. Our goal is modest, and that is to compare the dilutional effect of the different blood product ratios within the modern MTP paradigm. However, even though the results of simulations within the prescribed conditions are mathematically indisputable, they are generally not fully representative

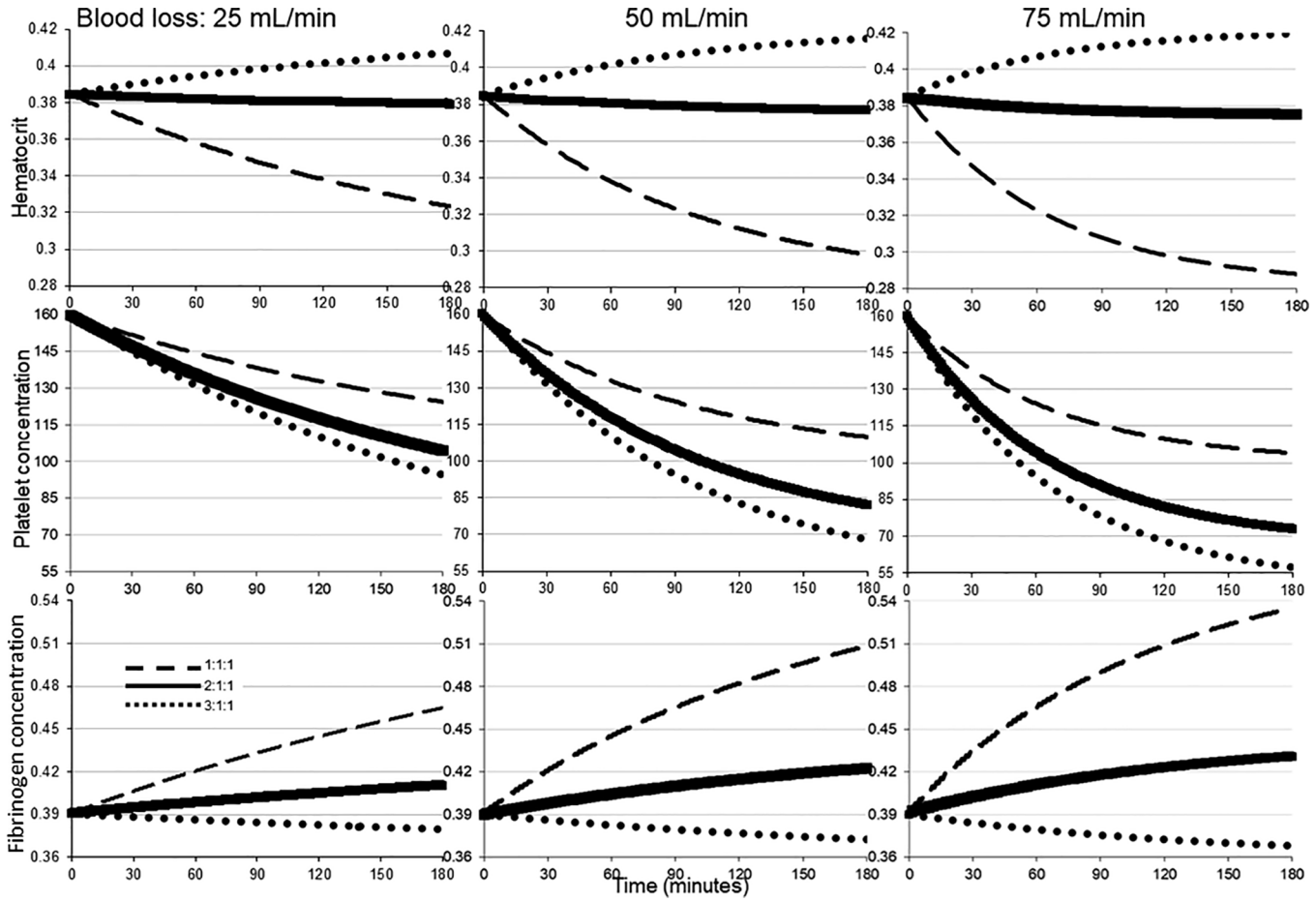

Fig. 2. Scenario 4–6. Initial blood loss 3 L; by time 0, intravascular volume has been restored with 1.5 L of PRBC and crystalloid. From time 0, hemorrhage and transfusion with PRBC:plasma:platelet ratio of 1:1:1, 2:1:1, and 3:1:1 at 25, 50, and 75 mL/min.

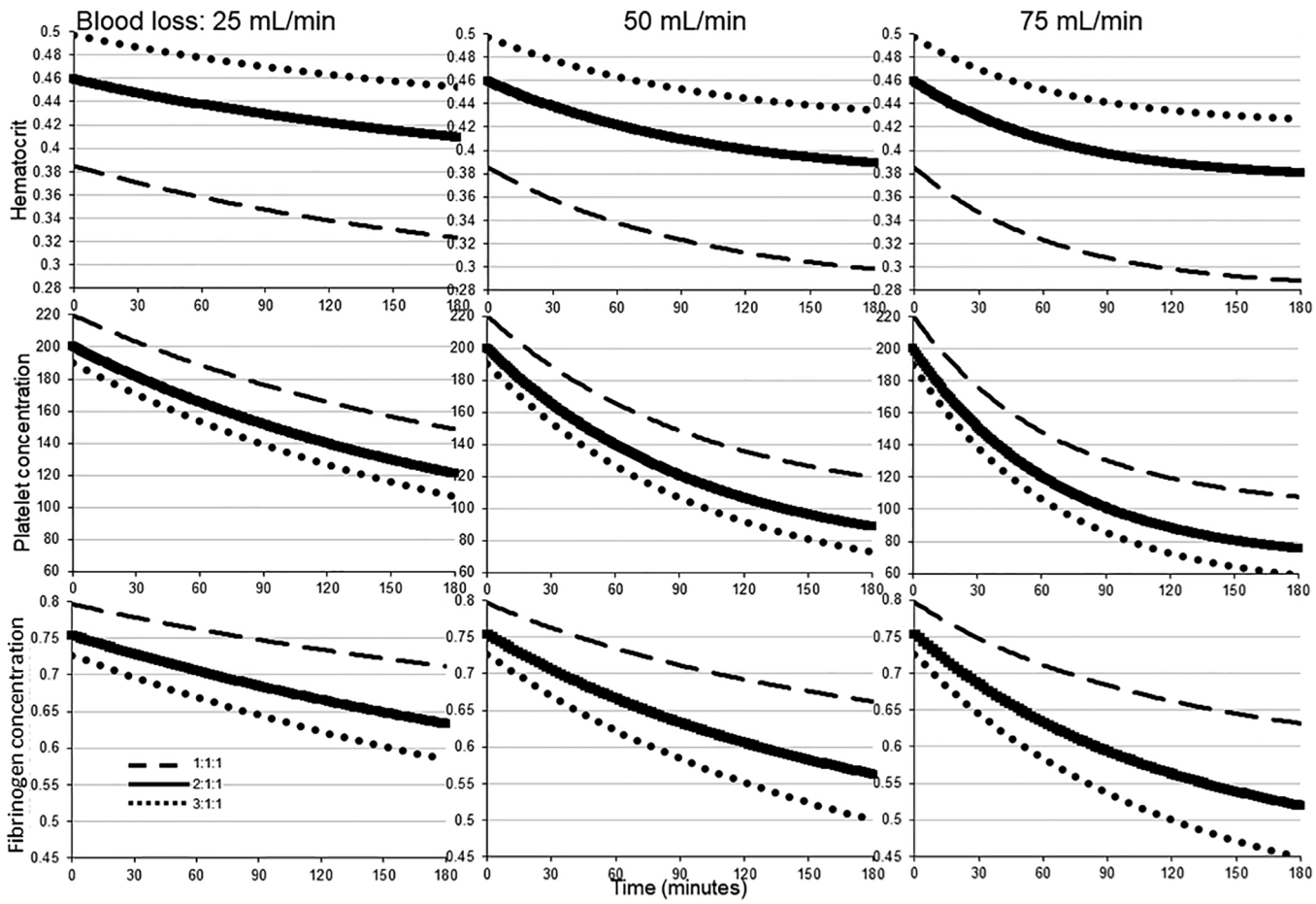

Fig. 3. Scenario 7–9. Initial blood loss 3 L; by time 0, intravascular volume has been restored with 3 L of blood products at 1–3:1:1 ratios. From time 0, hemorrhage and transfusion with the same blood product ratio as the initial resuscitation continues at 25, 50, and 75 mL/min.

of complex clinical scenarios. Pertaining to this exercise, how dilution interacts with hemostatic deficiency caused by tissue hypoperfusion, hypothermia, acidosis, consumption, interchange of clotting factors between the extra- and intravascular compartments, release of preformed and/or newly synthesized clotting factors from the liver, and release of platelets from the splenic pool is unknown. Furthermore, apart from the wide variation in clotting factor levels between healthy individuals, it is not certain, even in an individual, that baseline levels of all other clotting factors are the same. Nor is it certain that the consumption of clotting factors during critical/massive hemorrhage is similar. Therefore, even though our simulation is on fibrinogen alone and that we are only comparing the dilutional effects of different blood product ratios, our results must be interpreted with caution. Our model assumes the intravascular volume is maintained at 5 L after initial resuscitation. This is not representative of all bleeding patients but is a goal strived for, often successfully eventually, especially in surviving patients. In the present simulation exercise, although we calculated the blood parameters by the minute, our conclusion should be applicable as long as the average volume over longer time intervals is maintained normal. Finally, our model does not incorporate the option of administering select coagulation factors in concentrated forms. Use of these factors under the guidance of thromboelastography has shown promise but has yet to reach widespread acceptance in major shock management because tailored factor replacement does not in itself address the need for volume, especially during the initial phase of resuscitation.

In conclusion, computer simulation of a dilutional hemorrhagic model suggests that in non-severe shock, the differences between 1:1:1, 2:1:1, or 3:1:1 during the initial resuscitation phase may be relatively small. When resuscitation is initiated and sustained with a 3:1:1 ratio, hematocrit becomes supranormal; otherwise the hematocrit stays within physiologic/adequate range with the other scenarios simulated. In severe shock, starting early with a balanced ratio close to 1:1:1 is desirable as it leads to the least deficiency in FC and platelets. For major surgery and no doubt for ongoing severe traumatic hemorrhage, FC well above 50% or even close to 100% is recommended (which also applies for *all* coagulation factors), especially if such conditions as hypothermia, acidosis, consumption coagulopathy, and logistic delays in delivering blood products are present, until bleeding is controlled. Our recommendation of 1:1:1 is based in part on this argument. Regardless of the blood ratio, the platelet count drops over time. Fortunately, replenishing platelets is relatively easy. Furthermore, platelets are often supplied in adult packs each of which contains 4–6 units of platelets, making platelets less likely than plasma to be under-used. We believe that our results on the superiority of a 1:1:1 ratio for the most severe hemorrhagic situations are consistent with the increasingly recognized benefits of using whole blood in severe military and civilian trauma [20]. When in doubt, start with 1:1:1 until further guidance from test results and clinical observation suggest otherwise. For centers where the massive transfusion pack consists of blood product ratios of 3:1:1 (as opposed to 1:1:1), our simulation results, subject to confirmation by experimental trials, suggest that supplemental plasma and platelets may be prudent when resuscitating patients with severe hemorrhage.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Author contributions

AMHH conceived the study, analyzed and interpreted the data, drafted and revised the manuscript. **AKH** drafted and revised the manuscript, created the figures, and approved the final version for publication. **GBM** analyzed the data, drafted and revised the manuscript, and formatted it according to Journal's requirements. All authors approved the final version for publication.

CRediT authorship contribution statement

Anthony M.-H. Ho: Conceptualization, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Adrienne K. Ho:** Formal analysis, Writing - review & editing. **Glenio B. Mizubuti:** Formal analysis, Writing - review & editing.

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