Crystalloid infusion rate during fluid resuscitation from acute haemorrhage

T. Tatara*, T. Tsunetoh and C. Tashiro

Department of Anaesthesiology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan

*Corresponding author. E-mail: ttatara@hyo-med.ac.jp

Background. Information is lacking concerning optimal infusion rates of crystalloid during resuscitation from acute haemorrhage. In this study, a mathematical model was used to predict infusion volume of crystalloid needed to restore and maintain blood volume after acute haemorrhage.

Methods. The scenario was a haemorrhage of 15 ml kg\(^{-1}\) over 30 min in a 70 kg man. A bolus of crystalloid was administered at a rate of 40, 60, 80, 100, or 120 ml kg\(^{-1}\) h\(^{-1}\) until blood volume was restored. Fluid infusion rate needed to maintain blood volume for a further 1 h was computed.

Results. Blood volume was restored earlier at high bolus infusion rates compared with low bolus infusion rates (6 min at 120 ml kg\(^{-1}\) h\(^{-1}\) vs 63 min at 40 ml kg\(^{-1}\) h\(^{-1}\)). Fluid infusion rates for blood volume maintenance approached 33 ml kg\(^{-1}\) h\(^{-1}\) irrespective of bolus infusion rates. The restoration fluid volume at 40 ml kg\(^{-1}\) h\(^{-1}\) was 2.9 litre, three times that at 80–120 ml kg\(^{-1}\) h\(^{-1}\). The maintenance fluid volume at 80–120 ml kg\(^{-1}\) h\(^{-1}\) was 2.9 litre, 0.6 litre more than that at 40 ml kg\(^{-1}\) h\(^{-1}\). During the blood volume maintenance, the interstitial volume increased to 3.8 litre above normal at 40 ml kg\(^{-1}\) h\(^{-1}\) and to 2.5 litre at 80–120 ml kg\(^{-1}\) h\(^{-1}\).

Conclusions. Bolus crystalloid infusion exceeding 80 ml kg\(^{-1}\) h\(^{-1}\) may not increase effectiveness of fluid resuscitation. Crystalloid resuscitation for more than 2 h may be detrimental in view of an excessive net fluid retention.

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Administration of crystalloid solution is the first line therapy for treating acute haemorrhage during the perioperative period.\(^1\) It is considered that the replacement volume of crystalloid solution required is three- to four-fold the blood volume loss on the basis that only 20% of administered crystalloid fluid will remain in the intravascular space.\(^2\)\(^3\)

However, this scenario may not be sufficiently valid for clinical practice because in most previous studies\(^1\)–\(^6\) fluid was infused into subjects over a limited period of time (i.e. 5–30 min). The reality of crystalloid resuscitation is that acute haemorrhage is usually treated by a bolus infusion of crystalloid solution followed by a continuous infusion. Nevertheless, little information is available concerning optimal fluid infusion rates during crystalloid resuscitation from acute haemorrhage.\(^5\)\(^7\)

A mathematical model of microvascular exchange describing the dynamic distribution and transport of fluid and proteins can improve our understanding of time-dependent fluid dynamics and the impact of different fluid regimens.\(^8\)–\(^11\) By using such a model, it is also possible to predict fluid infusion rates needed to maintain blood volume constant. Because of the difficulties in performing controlled studies in patients with acute bleeding,\(^12\) the model may help us to better understand the clinical practice of crystalloid resuscitation. The aim of this study was to use the model to compare the effects of different rates of crystalloid bolus fluid infusion on the overall crystalloid volumes necessary for the restoration and maintenance in blood volume after acute haemorrhage.

Methods
The model used was based on the microvascular exchange model proposed by Bert and colleagues\(^8\) and Gyenge and...
Intracellular components were not taken into account because extracellular fluid spaces are central to fluid volume changes during perioperative periods. The microvascular exchange model predicts fluid and protein distribution and transport in the vascular and interstitial compartments, and lymphatics. For simplicity, all proteins in the modelled system were assumed to have the same properties as albumin. Urinary dynamics were included in the model formulation. Because the original model assumed the capillary membrane to be relatively impermeable to water and protein, the whole-body values for conductivity portions in the fluid filtration coefficient ($k_F$) and the permeability–surface area product for protein (PS) were estimated by fitting the calculated time-course in plasma dilution to the experimental data in Drobin and Hahn using a non-linear least-squares procedure. These data were obtained during the infusion of 25 ml kg$^{-1}$ Ringer’s acetate solution over 30 min into normovolaemic male volunteers (mean body weight 76 kg).

A schematic diagram of the compartments comprising the system and the transport paths of fluid and protein between them is shown in Figure 1. Table 1 provides normal steady-state values for fluid and protein in the compartments and parameters related to capillary exchange, lymphatics, and kidney in a 70 kg man.

![Fig 1 Schematic diagram showing the compartmental model of the body and the relevant mass flows of fluid and protein.](https://academic.oup.com/bja/article-abstract/99/2/212/313387)

**Table 1** Normal steady-state values for fluid and protein in the compartments and parameters related to capillary exchange, lymphatics, and kidney in a 70 kg man.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume, $V_{PL}$ (ml)</td>
<td>3200</td>
</tr>
<tr>
<td>Haematocrit, Hct (%)</td>
<td>40</td>
</tr>
<tr>
<td>Intervascular volume, $V_T$ (ml)</td>
<td>8400</td>
</tr>
<tr>
<td>Plasma hydrostatic pressure (mm Hg)</td>
<td>11</td>
</tr>
<tr>
<td>Plasma protein concentration (g ml$^{-1}$)</td>
<td>0.07</td>
</tr>
<tr>
<td>Interstitial protein concentration (g ml$^{-1}$)</td>
<td>0.0298</td>
</tr>
<tr>
<td>Lymph flow rate, $J_L$ (ml h$^{-1}$)</td>
<td>75.7</td>
</tr>
<tr>
<td>Rate of urine production, $J_U$ (ml h$^{-1}$)</td>
<td>60.0</td>
</tr>
</tbody>
</table>

Fluid balances:

$$\frac{dV_{PL}}{dt} = -J_{INF} - J_{IT} + J_L - J_U - J_{HEM} \left(1 - \frac{\text{Hct}}{100}\right) \quad (1)$$

$$\frac{dV_{IT}}{dt} = J_{IT} - J_L - J_{PER} - J_{ISL} \quad (2)$$

where the subscripts $\text{PL}$, $\text{IT}$, $\text{L}$, and $\text{U}$ denote the values in the variable in the plasma, interstitial, lymphatic, and urinary compartments, respectively; $d$ is the change; $t$ is time in hours; $V$ is the compartment volume in millilitres; $J_{INF}$ and $J_{HEM}$ are fluid infusion rate and haemorrhage rate in millilitres per hour; $J_{IT}$, $J_L$, and $J_U$ are the rates of fluid transfer from plasma to interstitium, rate of fluid transfer from interstitium to lymphatics, and rate of urine production in millilitres per hour, respectively; $J_{PER}$ and $J_{ISL}$ are the perspiration rate (i.e. $2.0 \text{ ml h}^{-1}$) and insensible water losses (i.e. $40.0 \text{ ml h}^{-1}$), respectively; Hct is haematocrit in per cent.

Protein balances:

$$\frac{dQ_{PL}}{dt} = -Q_{IT} + Q_L - Q_{HEM} \quad (3)$$

$$\frac{dQ_{IT}}{dt} = Q_{IT} - Q_L \quad (4)$$

where $Q$ is the protein content in grams; $Q_{IT}$ and $Q_L$ are the rates of protein transfer from plasma to interstitium and from interstitium to lymphatics in grams per hour, respectively; $Q_{HEM}$ is the rate of protein transfer by haemorrhage in grams per hour.

The rate of fluid filtration, $J_{IT}$, from the plasma to interstitial compartments is given by the Starling equation

$$J_{IT} = \left(k_F \frac{V_{PL}}{V_{PL,NL}} \right) \left[P_C - P_{IT} - \sigma (\pi_{PL} - \pi_{IT})\right] \quad (5)$$

where the subscripts $C$ and $NL$ denote the values in the variable in the capillary and in the normal steady state, respectively, $P$ is the hydrostatic pressure in mm Hg, and $\pi$ is the colloid osmotic pressure in mm Hg.

Hct was calculated by the mass balance in red blood cells associated with fluid infusion and haemorrhage. Details on how fluid and protein are transported...
between the plasma, interstitium, and lymphatics are given in references.8–11

Differential equations in \( V_{PL} \), \( V_{IT} \), \( Q_{PL} \), and \( Q_{IT} \) are solved with respect to \( t \) using the Runge–Kutta method.

To confirm the validity of the model, the comparison in time-course plasma dilution was made between experimental data in Drobin and Hahn5 and that predicted by our model during 25 ml kg\(^{-1}\) crystalloid infusion over 30 min in a 76 kg man when 900 ml of blood was withdrawn in 15 min.

For this study, fluid resuscitation with isotonic crystalloid solution was modelled for a 70 kg man. The scenario was a haemorrhage of 15 ml kg\(^{-1}\) over a 30 min period. A bolus in fluid was administered at the rate of 40, 60, 80, 100, or 120 ml kg\(^{-1}\) h\(^{-1}\) until blood volume was restored to the pre-haemorrhage level. Thereafter, crystalloid infusion rates needed to maintain blood volume for a further 1 h were computationally determined every 3 min. The fluid volumes necessary for the restoration and maintenance in blood volume were also calculated (i.e. restoration fluid volume and maintenance fluid volume) and compared for different bolus infusion rates.

The time-course in interstitial volume change and the rate in fluid filtration from the plasma to interstitial compartments (i.e. \( J_{IT} \)) were calculated during the period of maintenance of blood volume. To examine the contribution of hydrostatic and osmotic force to \( J_{IT} \), hydrostatic pressure differences (i.e. \( P_C – P_{IT} \)) and differences of effective colloid osmotic pressure [i.e. \( \sigma (\pi_{PL} – \pi_{IT}) \)] between capillaries and interstitium were also calculated.

### Results

The time-course of plasma dilution during crystalloid infusion into a normovolaemic man calculated by the mathematical model showed a good fit with the experimental data (Fig. 2A). Best-fit values of 299.6 (ml mm Hg\(^{-1}\) h\(^{-1}\)) for \( k_F \) and 201.4 (ml h\(^{-1}\)) for PS were calculated and subsequently used. The plasma dilution curve predicted by our model using these parameter values during crystalloid infusion after blood withdrawal also showed a considerable agreement with the experimental data (Fig. 2B).

Figure 3 shows the modelled time-course in crystalloid infusion rate and volume changes in fluid compartments during fluid resuscitation from a haemorrhage in 15 ml kg\(^{-1}\) over 30 min followed by a bolus infusion rate in 80 ml kg\(^{-1}\) h\(^{-1}\). Blood volume was restored to the pre-haemorrhage level 12 min after the start in fluid infusion. Thereafter, the fluid infusion rate necessary to maintain the blood volume gradually decreased to 33 ml kg\(^{-1}\) h\(^{-1}\). Compared with the pre-haemorrhage level, the interstitial volume had decreased by 210 ml at the end of the period in haemorrhage. However, by the end in the restoration and maintenance in blood volume period, crystalloid solution infusion had increased the interstitial volume to in excess of 2.6 litre of the pre-haemorrhage level. Urine output increased monotonically with time after the start of fluid infusion, reaching approximately 250 ml at the end of infusion.

Crystalloid infusion rates necessary to maintain blood volume decreased with time in an exponential manner after bolus infusion (Fig. 4A). As indicated by the abrupt decrease in fluid infusion rate required to maintain blood volume, blood volume was restored sooner at high bolus infusion rates compared with low bolus infusion rates (i.e. 6 min at 120 ml kg\(^{-1}\) h\(^{-1}\) vs 63 min at 40 ml kg\(^{-1}\) h\(^{-1}\)). However, at the end of the period of blood volume maintenance, fluid infusion rates had converged to around 33 ml kg\(^{-1}\) h\(^{-1}\) for all bolus infusion rates.

Figure 4B shows the comparison of restoration and maintenance fluid volumes for different bolus infusion rates. The restoration fluid volume at 40 ml kg\(^{-1}\) h\(^{-1}\) was 2.9 litre, which was 1.6 litre more than at infusion rates of 29.8 litre at 40 ml kg\(^{-1}\) h\(^{-1}\). In contrast, the maintenance fluid volume at infusion rates of 80–120 ml kg\(^{-1}\) h\(^{-1}\) was 2.9 litre, which was 0.6 litre more than at an infusion rate of 40 ml kg\(^{-1}\) h\(^{-1}\).

As shown in Figure 5, crystalloid infusion gave rise to a monotonic increase with time in interstitial volume during the period of maintenance of blood volume. The increase between the plasma, interstitium, and lymphatics are given in references.8–11

Differential equations in \( V_{PL} \), \( V_{IT} \), \( Q_{PL} \), and \( Q_{IT} \) are solved with respect to \( t \) using the Runge–Kutta method.

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in interstitial volume reached 3.8 litre for an infusion rate of 40 ml kg\(^{-1}\) h\(^{-1}\) compared with 2.5 litre at 80–120 ml kg\(^{-1}\) h\(^{-1}\). The time-course in changes in \(J_IT\) and hydrostatic pressure difference followed a similar pattern throughout the maintenance in blood volume, being large at 80–120 ml kg\(^{-1}\) h\(^{-1}\) compared with 40 ml kg\(^{-1}\) h\(^{-1}\). On the other hand, osmotic pressure differences were larger at 40 ml kg\(^{-1}\) h\(^{-1}\) compared with those measured at 80–120 ml kg\(^{-1}\) h\(^{-1}\).

**Discussion**

In this study, we have modelled the effects of different rates of bolus crystalloid fluid infusion on the time required to restore blood volume after acute haemorrhage, and on subsequent infusion rates to maintain blood volume. For the scenario, we chose a haemorrhage rate of 15 ml kg\(^{-1}\) over a 30 min period because the resultant blood loss volume is unlikely to result in a state of shock; a more severe rate in haemorrhage would require that fluid movement from the intracellular to extracellular space be taken into account because of a loss of cellular membrane function. Additionally, some of the model parameter values used for the prediction of fluid infusion rates may be subject to change by surgical trauma. Hormonal changes induced by surgical stress may contribute in part to a restoration of blood volume by decreasing urine output (i.e. rate of urine production) and thereby decrease fluid infusion rates necessary for fluid resuscitation. In contrast, changes of conductivity portions (i.e. fluid filtration coefficient, reflection coefficient for protein, and the permeability–surface area product for protein) induced by surgical trauma may require fluid infusion rates higher than those predicted in this study because more crystalloids administered leak from the plasma to the interstitium in the inflammatory state.\(^{11}\)

Model-fitted values of the fluid filtration coefficient \((k_F, 299.6 \text{ ml mm Hg}^{-1} \text{ h}^{-1})\) and the permeability–surface area product for protein (PS, 201.4 ml h\(^{-1}\)) are comparable with those (i.e. \(k_F=321.4 \text{ ml mm Hg}^{-1} \text{ h}^{-1}\); PS=200.7 ml h\(^{-1}\)) obtained by fitting our model to the experimental data of Connolly and colleagues\(^4\) of plasma
Considerable agreement between the experiment and model prediction of the time-course curves of plasma dilution in normovolaemic and haemorrhagic states (Fig. 2) lends support to the model’s validity. From the model, a haemorrhage of 15 ml kg\(^{-1}\) in a 70 kg man decreased blood volume by 830 ml (Fig. 3), which thereby suggests that 220 ml of fluid was mobilized from the interstitial space to the intravascular space (i.e. autotransfusion). This value of compensatory fluid volume is comparable with the 150 ml mobilization calculated after the withdrawal with 900 ml of blood in male volunteers.\(^5\)

Consistent with our expectation, the model demonstrated that less time was required to restore blood volume in response to a rapid bolus infusion of crystalloid solution compared with a slow bolus infusion (Fig. 4a). A bolus infusion rate of 40 ml kg\(^{-1}\) h\(^{-1}\) was the minimum infusion rate required to restore blood volume because the model predicted that continuous fluid infusion at a rate of 30 ml kg\(^{-1}\) h\(^{-1}\) or lower cannot restore blood volume at any time. Moreover, the restoration fluid volume was smaller at a bolus infusion rates of 80–120 ml kg\(^{-1}\) h\(^{-1}\) compared with a bolus infusion rate of 40 ml kg\(^{-1}\) h\(^{-1}\) (Fig. 4b). This finding can be attributed to the difference in fluid distribution between the intravascular and interstitial space. Namely, at the time of blood volume restoration, approximately 75–100% of the infused fluid remained in the intravascular space when the bolus infusion rate was 80–120 ml kg\(^{-1}\) h\(^{-1}\), whereas only 25% of the infused fluid did so at the bolus infusion rate of 40 ml kg\(^{-1}\) h\(^{-1}\).

In contrast, rapid bolus infusion increased the total maintenance fluid volume required compared with slow bolus infusion (Fig. 4b). In other words, compared with slow bolus infusion, rapid bolus infusion resulted in a high fluid infusion rate to maintain blood volume. Because lymph flow rate was one order of magnitude lower than the rate of fluid filtration from the plasma to interstitial compartments (\(J_{IT}\)), and urine volume was the same for different bolus infusion rates, these parameters are unlikely to be responsible for the high fluid infusion rates required after rapid bolus infusion. The finding is reasonably well explained by the high \(J_{IT}\) when fluid is rapidly infused (Fig. 5). A rapid bolus infusion of 80 ml kg\(^{-1}\) h\(^{-1}\) restored blood volume without significantly elevating interstitial fluid pressure (i.e. from −1.1 to −0.5 mm Hg), whereas slow bolus infusion of 40 ml kg\(^{-1}\) h\(^{-1}\) increased it from −1.1 to 1.4 mm Hg at the time of blood volume restoration. Because plasma hydrostatic pressure at the time of blood volume restoration was the same for all bolus infusion rates (i.e. 13 mm Hg), a large hydrostatic pressure difference between capillaries and interstitium for a rapid bolus infusion resulted in a high \(J_{IT}\) (Equation 5). A small osmotic pressure difference between plasma and interstitium for a rapid bolus infusion, resulting in a decrease of extraction of fluid from the interstitium to the intravascular space, also contributes in part to a high \(J_{IT}\). Rapid bolus infusion thus requires more fluid to maintain blood volume than does a slow bolus infusion. This difference in fluid infusion rates for the different bolus infusion rates disappeared at the end of the blood volume maintenance period (Fig. 4a). The apparent discrepancy can be attributed to the finding that \(J_{IT}\) was similar for different bolus infusion rates at the end of the period of blood volume maintenance (Fig. 5). This is because interstitial hydrostatic pressure does not change significantly with interstitial volume because of a high compliance in the overhydrated region of interstitium.\(^8\)–\(^10\)

The absolute values of fluid infusion rates and resultant fluid volume to restore and maintain blood volume may not be sufficiently valid for the individual patient because many parameter values in the model are derived from

(volume increase during saline infusion in sheep.\(^1\) Considerable agreement between the experiment and model prediction of the time-course curves of plasma dilution in normovolaemic and haemorrhagic states (Fig. 2) lends support to the model’s validity. From the model, a haemorrhage of 15 ml kg\(^{-1}\) in a 70 kg man decreased blood volume by 830 ml (Fig. 3), which thereby suggests that 220 ml of fluid was mobilized from the interstitial space to the intravascular space (i.e. autotransfusion). This value of compensatory fluid volume is comparable with the 150 ml mobilization calculated after the withdrawal with 900 ml of blood in male volunteers.\(^5\)

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![Fig 5 Time-course of interstitial volume change (A), rate of fluid transfer from plasma to interstitium (\(J_{IT}\)) (B), and hydrostatic pressure (C), and colloid osmotic pressure (D) differences between capillaries and interstitium during crystalloid resuscitation from a simulated haemorrhage of 15 ml kg\(^{-1}\) over 30 min in a 70 kg man. Time 0 represents when blood volume was restored to the pre-haemorrhage level.](https://academic.oup.com/bja/article-abstract/99/2/212/313387/216)
animal experiments and may be subject to inter-individual differences. However, a relative comparison of these values for different bolus infusion rates of crystalloid did demonstrate that even though blood volume is soon restored by rapid bolus infusion, aggressive crystalloid resuscitation needs to be continued during the maintenance of normal blood volume. Because the model deals only with fluid volume in fluid compartments, the model’s results do not fully reveal the optimal rate of crystalloid bolus infusion for fluid resuscitation. However, it should be noted that bolus infusion exceeding a rate of 80 ml kg\(^{-1}\) h\(^{-1}\) may not increase the overall effectiveness of fluid resuscitation because infusion at such rates does not significantly decrease the overall volume of fluid infused for restoration and maintenance of blood volume, or the volume of interstitial fluid accumulation. This is not the case with severe haemorrhage which continues for 30 min after the start of fluid resuscitation (i.e. a haemorrhage of totally 30 ml kg\(^{-1}\) over a 60 min period). In such a scenario, our model predicts that aggressive bolus infusion of 120 ml kg\(^{-1}\) h\(^{-1}\) largely reduces the overall volume of fluid infused (i.e. 7.5 litre) compared with 9.8 litre at the bolus infusion rate of 80 ml kg\(^{-1}\) h\(^{-1}\). A controlled clinical study is required to fully validate the conclusion.

Irrespective of bolus infusion rates, the crystalloid infusion rate reached a relatively high value, 33 ml kg\(^{-1}\) h\(^{-1}\), at the end of the period of blood volume maintenance. Continuous fluid administration at this rate of infusion increases the interstitial volume with time almost at a fixed rate. As a consequence, the model predicts that 2 h from the start of fluid resuscitation, interstitial fluid accumulation reaches 50% of the normal interstitial volume with a net fluid retention of ~4 litre. Such a large net fluid retention may cause significant side-effects in several-organ systems, with impaired pulmonary function being one such outcome. This contrasts with the finding when 5% albumin solution is used as resuscitation fluid instead of crystalloid solution. Our model predicts that the overall volume of 5% albumin required to restore and maintain blood volume is 1.7 litre with a net fluid retention of only 0.4 litre at bolus infusion rates of 40–120 ml kg\(^{-1}\) h\(^{-1}\). Based on the model’s results, rational fluid resuscitation would require recognizing that crystalloid resuscitation for more than 2 h may be detrimental to a patient. Alternative treatment modalities such as the early use of vasopressor agents should be considered to support haemodynamics.

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