The Rational of Colloid Requirements in Burn Patients: Literature Reviews

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**Backgrounds:** For decades, fluid resuscitation in burn patients has been done as a routine process; most clinicians continue to adjust volume requirements using Parkland formula for the initial 24-hour period. In a variety of situations, there is increasing recognition of using significantly greater volumes than anticipated by the Parkland formula; clinicians tend to escalate volume requirements to drive the urine output to the higher end of any desired range. This excessive fluid could result in numerous edema-related complications, which currently coined as “fluid creep” phenomenon. Besides optimizing titration of fluid infusion rate, there have been studies of earlier and more liberal use of colloids, and even the use of hypertonic saline. The overall goal is to reduce the resuscitation volume requirements and subsequently, early edema formation.

**Conclusion:** Current research in fluid resuscitation now concentrates on approaches to minimize fluid creep, including tighter control of fluid infusion rate. The single most important principle in using the Parkland formula, however, is that it should be used only as a guideline. The resuscitation rate and volume must be continually adjusted based on the response of the patient. Studies have been demonstrated to compare the use of crystalloids with early colloid in the first 24 hours post burn. At present, there are still wide variations in the timing of colloid resuscitation. However, use of 5% albumin in the second 24 hours seems to be an acceptable alternative.

**Latar Belakang:** Dalam dekade terakhir, resusitasi cairan pada pasien luka bakar telah dilakukan sebagai proses yang rutin; kebanyakan klinisi menggunakan rumus Parkland dalam 24 jam pertama untuk menyesuaikan volume cairan yang diberikan. Sesuai dengan variasi situasi pada pasien luka bakar, penggunaan volume cairan yang berlebih cenderung terjadi untuk meningkatkan pengeluaran urin. Pemberian cairan yang berlebih dapat mengakibatkan komplikasi edema yang dikenal dengan fenomena “fluid creep”. Banyak penelitian yang telah dilakukan untuk optimasi titrasi dan jenis cairan yang digunakan, seperti pemakaian koloid atau larutan garam hipertonik. Tujuannya adalah untuk menurunkan kebutuhan volume cairan dan terjadinya edema.


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the urine output to the higher end of any desired range\textsuperscript{1,2}.

This excessive fluid could result in numerous edema-related complications, which discussed briefly as “fluid creep” phenomenon\textsuperscript{3}. Significant edema has becoming the hallmark of moderate to large burn injuries, and it is worsened by excessive fluid resuscitation itself. The consequences of this increased fluid administration include airway swelling, secondary abdominal compartment syndrome, soft tissue edema in the extremities necessitating more frequent escharotomies and even fasciotomies, elevated intraocular pressures, and an overall increased risk of death. Current research in fluid resuscitation now concentrates on approaches to minimize fluid creep, including tighter control of fluid infusion rate. The single most important principle in using the Parkland formula, however, is that it should be used only as a guideline. The resuscitation rate and volume must be continually adjusted based on the response of the patient. Besides optimizing titration of fluid infusion rate, there have been studies of earlier and more liberal use of colloids. The overall goal is to reduce the resuscitation volume requirements and subsequently, early edema formation.

It is recognized for years, concerning about the loss of capillary membrane integrity and leakage of delivered proteins into the interstitial space, we tend to avoid colloids in the first 24-hour period and reliance on a pure crystalloid approach for the first 24 hours. Studies have been demonstrated to compare the use of crystalloids with early colloid in the first 24 hours postburn. At present, there are still wide variations in the timing of colloid resuscitation. However, the important theme about this article is to familiarize the current concept in resuscitation strategies, and understanding the earlier use of colloid as the new approach in minimizing the fluid creep prevalence.

**Burn Shock and Edema Formation**

Burn shock is a form of hypovolemic shock that arises as a result of the translocation of isotonic protein-containing fluid from the vascular space into the interstitial space, resulting in edema\textsuperscript{5}. Significant edema is the hallmark of moderate to large burn injuries, and is worsened by fluid resuscitation itself\textsuperscript{6,7}. When burn size approaches 25% TBSA or greater, edema also forms in the non-burned soft tissues distant from the burn wound, including the lung, muscles, and intestines\textsuperscript{8,9}. Direct thermal damage is partly responsible for this alterations in the burn wound, locally released inflammatory mediators, also play an even more significant role, neutrophils, oxygen-free radicals, prostaglandins and leukotriens, kinins, serotonin, and histamine are all implicated in the pathogenesis of edema formation postburn injury\textsuperscript{5}.

**Starling Forces**

The force that controls the movement of fluid across the capillary membrane was clearly explained by Starling in 1896\textsuperscript{10}. This well-known Starling equation:

\[
Q = K_f (P_{cap} - P_i) + \sigma (\pi_p - \pi_i)
\]

Q is the fluid filtration rate, the rate at which fluid moves from the vascular space, across the capillary membrane, into the interstitial space. Under normal circumstances any fluid entering the interstitium is equally removed by the lymphatics, so that edema does not form.

\(K_f\) is the fluid filtration coefficient, a measure of how easily fluid is able to move across the capillary membrane and into the interstitial space. This depends on the properties of the capillary membrane, especially the surface area of the capillary membrane (larger areas facilitate movement), and the actual compliance of the interstitium\textsuperscript{5}. This compliance depends on the structural integrity of the collagen fibers, the hyaluronic acid linkages between them, and the density and hydration of the ground substance in which these molecules are embedded.

\(P_{cap} - P_i\) is the gradient in hydrostatic pressure between the capillary pressure (\(P_{cap}\)) and the interstitial hydrostatic pressure (\(P_i\)). This gradient is in a direction favoring fluid movement out of the capillary into the interstitium. A higher gradient, caused by an elevation of \(P_{cap}\) or a reduction in \(P_i\) pushes more fluid out and increases \(Q\).

\(\pi_p - \pi_i\) is the colloid osmotic pressure gradient representing the difference between
the plasma colloid osmotic pressure (\(\pi_p\)) and the interstitial colloid osmotic pressure (\(\pi_i\)). This gradient is in the direction favoring fluid retention within the capillary because of the higher concentration of protein within the plasma relative to that in the interstitial space. This colloid osmotic pressure gradient is an opposing force for the hydrostatic gradient, so fluid would not continually seep out of the capillary into the interstitium and edema does not normally develop. If \(\pi_p\) were to decrease significantly, as in hypoproteinemic state, this decrease in colloid osmotic gradient allows increased fluid flux into the interstitial space\textsuperscript{5}.

\(\sigma\) is the coefficient represents the degree of capillary membrane permeability. An impermeable membrane has a \(\sigma\) of 1, whereas a freely permeable membrane has a \(\sigma\) of 0. Normal dermal capillaries have a \(\sigma\) of 0,95.

**Starling Forces in Burn Patients**
As seen on Figure 1. Fluid filtration rate (Q) is dramatically increases immediately, most notably in the first 1 to 2 hours post injury, reaches a plateau by 24 hours, and then although remaining elevated above normal, gradually declines over the next few days\textsuperscript{5,7,11}.

In burn patients, there are altered Starling forces in the burn wound itself and in non burn soft tissues, which primarily correlated with the capillary permeability. Capillary permeability (\(\sigma\)) increases significantly in the microcirculation within and surrounding the burn wound, in the dermis \(\sigma\) drops numerically from 0,9 (nearly impermeable) to 0,3 (highly permeable). In burn wound, the capillary membrane becomes permeable to many plasma proteins including albumin and small-to-moderate sized globulins. This permeability increase is most profound acutely and may remain elevated for several days post burn\textsuperscript{5,9,11-13}.

While in non burn soft tissues, within the first few hours postburn, there is an increase in capillary permeability, which may be caused by the systemic dissemination of inflammatory mediators\textsuperscript{14-16}, but this change is transient and capillary permeability soon returns to normal. The most important alteration is the loss of plasma colloid osmotic pressure as a result of the hypoproteinemic state that develops with burns greater than or equal to 25% to 30% Total Body Surface Area (TBSA). Correction of the hypoproteinemic state with infusions of albumin or plasma hinders the development of
The increasing compliance of the interstitium contributes to the increasing of the $K_f$ related to the destruction of the collagen framework and surrounding matrix, which normally restricts fluid influx. Furthermore, as edema progresses, hydration of the matrix increases the compliance because the swelling mechanically disrupts bonds between various macromolecules. A self-perpetuating cycle is created in which edema leads to more edema formation, allowing large increases in interstitial volume with relatively little increase in its hydrostatic pressure, which will be described below.

There is a small and transient increase in $P_{cap}$ immediately following the burn, but more importantly there is a profound decrease in $P_i$ from its usual value of -2 to +2 mmHg to as low as -20 to -40 mmHg. This is believed to occur because the framework of collagen and hyaluronic acid is unraveled by burn and inflammation, produces fragmentation of these molecules into osmotically active particles. The end result is that, much like a compressed sponge that is allowed to expand, the interstitium draws fluid into itself by creating a negative, transient yet powerful “sucking” or “vacuum” force, lowering $P_i$ and dramatically increasing the $P_{cap} - P_i$ gradient.

As fluid expands the interstitium, $P_i$ begins to rise again and returns to a slightly positive value within a few hours. As described previously, however, because of the increased interstitial compliance, interstitial pressures do not rise with this volume increase to the degree that happens in the normal state.

$\pi_p - \pi_o$, the osmotic pressure gradient, begins to decrease following burn injury, occurs as a result of decreasing plasma protein concentration caused by leakage of protein across the now highly permeable plasma membrane ($\pi_p$ decreases), and by a gradual increase in $\pi_i$ as plasma proteins and other osmotically active particles accumulate in the interstitium.

In recent years, there has been increasing recognition of using significantly greater volumes than anticipated by the Parkland formula. The single most important principle in using the Parkland formula, however, is that it should be used only as a guideline. The resuscitation rate and volume must be continually adjusted based on the response of the patient.

It seems that clinicians tend to escalate volume requirements to drive the urine output to the higher end of any desired range. This excessive fluid could result in numerous edema-related complications. The consequences of this increased fluid administration, airway swelling, secondary abdominal compartment syndrome, soft tissue edema in the extremities necessitating more frequent escharotomies and even fasciotomies, elevated intraocular pressures, and an overall increased risk of death, is worsened by excessive fluid resuscitation itself.

Current research in fluid resuscitation now concentrates on approaches to minimize fluid creep, including tighter control of fluid infusion rate and studies of earlier and more liberal use of colloids. The overall goal is to reduce the resuscitation volume requirements and subsequently, early edema formation.

### Overview of Colloid Resuscitation

Important themes about colloid resuscitation that need to be discussed throughout this article are the reasoning to allow the use of colloid in burn resuscitation, the most appropriate time to use colloids, and also trying to find the kind and concentration of colloid best used in fluid resuscitation.

There are two reasons why we recommend the allowance of using colloids in burn patients. First, correction of the hypoproteinemic state with infusions of albumin or plasma hinders the development of non-burn soft tissue edema, including the lung edema.

Surprisingly, there is a difference in altered Starling forces in the burn wound itself and in non-burn soft tissues, which primarily correlated with the capillary permeability. In burn wound, the capillary membrane becomes permeable to many plasma proteins including albumin and small-to-moderate sized globulins. This perme-ability increase is most profound acutely and may remain elevated for several days postburn. While in non-burn soft tissues,
Within the first few hours post burn, there is an increase in capillary permeability, which may be caused by the systemic dissemination of inflammatory mediators, but this change is transient and capillary permeability soon returns to normal\textsuperscript{14-16}. Demling et al. studied the edema process in burned and non-burned tissues including the lung, in the adult sheep. They used lymph flow (QL) and the lymph-plasma (L/P) protein ratio as indicators of the rate of fluid and protein flux across the microcirculation and into the interstitium. They found that there is an increase of QL in both burn and non-burned tissues, including the lung. While the L/P protein ratio was found highly increased in burned tissues, the L/P protein ratio in non-burned tissues, including the lung decreased or remained at baseline, indicating the edema process in non-burned tissues, including the lung, would be due to hypoproteinemic state with no change in protein permeability and could be corrected by restoration of plasma proteins\textsuperscript{9,17}. It was also stated, this hypoproteinemic state develops with burns greater than or equal to 25\% to 30\% TBSA\textsuperscript{8}.

The second reason is, colloids do seem to reduce the overall volume requirements compared with use of crystalloid alone. Two randomized prospective studies have compared crystalloids with early colloid in the first 24 hours postburn. Goodwin and colleagues in 1984 randomized 79 adult burn patients to resuscitation with RL or 2.5\% albumin in RL solution. The crystalloid-treated patients required more fluid for successful resuscitation than did those receiving colloid solutions (3.81 vs. 2.98 mL/kg/%TBSA burn, with p < 0.01)\textsuperscript{22}. O’Mara and colleagues randomized 31 adult burn patients to resuscitation with a RL infusion or to 2 L of RL infused over 24 hours combined with an adjustable infusion 75 mL/kg of fresh frozen plasma. The colloid group required significantly less resuscitation fluid to achieve the urine output endpoint (0.21 L/kg vs. 0.26 L/kg, with p < 0.005)\textsuperscript{23}. From these two studies, it can be safely concluded that early colloid provision reduces overall resuscitation volume requirements and early edema formation.

Besides the supportive reasons of using colloids in burn resuscitation, there are also some studies which still question whether this colloids might translate to benefits, such as improved survival. In their study, Liberati and colleagues found that for patients with hypovolemia there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline, and there is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia\textsuperscript{24}. Cooper et al randomized eligible adults (>15 years) suffering from thermal injury not more than 12 hours before enrollment, received fluid resuscitation with Ringer’s lactate (n=23) or 5\% human albumin plus Ringer’s lactate (n=19) by protocol, to achieve recommended (American Burn Association) resuscitation endpoints. This trial conclude that treatment with 5\% albumin from day 0 to day 14 does not decrease the burden of MODS (Multiple Organ Dysfunction Syndrome) in adult burn patients\textsuperscript{25}. Zdolsek and colleagues by their trial in National Burn Unit in a Swedish university hospital, also concluded that albumin supplementation during the first week after a burn does not mobilise tissue edema in humans\textsuperscript{26}. Cochrane reviews has discussed about this human albumin solution for resuscitation and volume expansion in critically ill patients, and found that there is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia. The possibility that there may be highly selected populations of critically ill patients in which albumin may be indicated remains open to question. However, in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonable that albumin should only be used within the context of well concealed and adequately powered randomised controlled trial. For burns, the relative risk was 2.40 (1.11, 5.19)\textsuperscript{27}.

The next issue that we need to evaluate is the appropriate time in strategy of giving colloids. Baxter recommended the administration of colloid during the second 24-hour period postburn, with the amount of colloid required varied between 0.3 and 0.5 mL/kg/%TBSA.
burn, he argued that this amount is sufficient to re-expand the plasma volume in most patients where the capillary leak would be sealed by 24 hours\textsuperscript{28,29}. Goodwin and colleagues assess the effects of crystalloid and colloid resuscitation on hemodynamic response and on lung water following thermal injury, 79 patients were assigned randomly to receive Ringer’s lactate solution or 2.5% albumin-Ringer’s lactate solution. Although crystalloid-treated patients required more fluid for successful resuscitation (3.81 vs. 2.98 mL/kg/%TBSA burn, with \( p < 0.01 \)), it is however noted that lung water remained unchanged in the crystalloid-treated patients (\( p > 0.10 \)), but progressively increased in the colloid-treated patients over the seven day study (\( p < 0.0001 \)). They concluded that the addition of colloid to crystalloid resuscitation fluids, especially before 24 hours, produces no long lasting benefit and promotes accumulation of lung water\textsuperscript{22}.

Evans et al. advocate immediate colloids on the basis that these help to maintain intravascular volume. They suggest the use of normal saline at 1 mL/kg/%TBSA burn, 2000 mL 5% Dextrose, and colloid at 1 mL/kg/%TBSA burn in the first 24 hours\textsuperscript{30}. Fodor et al also stated that protein-based colloids are included in most of the formulae and the beneficial effect is considered to be higher than the potential side effects. They are in favor of administering colloids during the resuscitation period for major burns, starting in the early period after injury\textsuperscript{31}.

The Demling group takes an intermediate approach and gives colloids at 8 to 12 hours post injury arguing that normal capillary permeability is restored in non-burn soft tissues by 8 to 12 hours and that hypoproteinemia is the major cause of ongoing edema formation at this time\textsuperscript{9,17}. In his article, Robert Oliver also wrote that until now, there is no single recommendation has been distinguished as the most successful approach in resuscitative fluid management. An important consideration for adding colloid in the first 24 hours is the loss of capillary integrity during early burn shock. This process occurs early and is present for 8-24 hours depending on which authority is referenced. A strategy for testing whether the capillary leak has begun to resolve involves substituting an equal volume of albumin solution for RL solution. An increase in urine output suggests that at least some of the leak has resolved and that the further introduction of colloid can help decrease the fluid load. Guidelines for this infusion have been reported as 0.5-1 mL/kg/% TBSA burn during the first 24 hours, beginning 8-10 hours postburn as an adjuvant to RL solution resuscitation. The US Army Institute of Surgical Research uses a similar approach but stratifies the albumin calculations by the estimated TBSA of the burn. For burns of 30-50\%, they use 0.3 mL/kg per percentage burn; for burns of 50-70\%, 0.4 mL/kg per percentage burn is used; and for burns of 70\% and greater, they use 0.5 mL/kg per percentage burn\textsuperscript{32}.

JTTS clinical practice guidelines recommends albumin 5%-25\% for burn care, started at 12 hour mark for large resuscitation, and for normal resuscitation, starts at the 24 hour mark. While, Chung et al. in their journal correlating about evolution of burn resuscitation in operation Iraqi freedom, clearly agreed to use albumin 5\% at 12 to 18 hours after burn injury if the projected 24-hour resuscitation requirement exceeds 6 mL/kg/%TBSA burn, as described in Emergency War Surgery Handbook\textsuperscript{33}.

Most of the mainstream burn formulas add colloid during the resuscitation, at least in the second 24-hour period. However, what must be recognized is that despite a general consensus that colloid use is both beneficial and appropriate, especially in burns greater than 40\% TBSA, demonstrating improved outcomes in morbidity or mortality has been difficult. The rationale for this is the massive protein losses that have occurred from the burn wound during the first 24 hours.

The last issue is to find the answer for the kind of colloid best used in burn resuscitation. Albumin, as the plasma protein that most contributes to intravascular oncotic pressure, when administered intravenously as a 5\% solution from pooled plasma product, approximately half the volume remains intravascularly, as opposed to 20-30\% of crystalloid solutions\textsuperscript{32}. 
Replacing the deficit from the massive protein losses with a steady infusion of 5% or 25% albumin solution can serve to maintain a serum albumin concentration greater than 2 g/dL, which can help reduce tissue edema and improve gut function.

Albumin is a highly soluble, ellipsoidal protein (MW 66,500), accounting for 70-80% of the colloid osmotic pressure of plasma. It is, therefore, important in regulating the volume of circulating blood. Albumin (human), 5% solution, supplies the oncotic equivalent of approximately its volume of normal human plasma. Albumin (human), 25% solution, supplies the oncotic equivalent of approximately five times its volume of human plasma. When injected intravenously, 5% albumin will increase the circulating plasma volume by an amount approximately equal to the volume infused. When injected intravenously, 25% albumin will draw approximately 3.5 times its volume of additional fluid into the circulation within 15 minutes, if the recipient is adequately hydrated. In both solutions this extra fluid reduces hemoconcentration and decreases blood viscosity.

To a lesser extent, the use of nonprotein colloid solutions, such as Dextran, Pentastarch, or Hetastarch, in burn resuscitation has also been described. Dextran is a complex, branched glucan (polysaccharide made of many glucose molecules) composed of chains of varying lengths (from 10 to 150 kilodaltons). It is used medicinally as an antithrombotic (anti-platelet), to reduce blood viscosity, and as a volume expander. While hydroxyethyl starches are typically described by their average molecular weight, typically around 130 to 200 kilodaltons. Over two decades ago, Demling and colleagues, in an animal model, demonstrated that burn resuscitation with Dextran 40 (low-molecular-weight Dextran) maintained hemodynamic variables and urine output with significantly less fluid and significantly less non-burn tissue edema, than with RL alone. This was caused by an increase in the colloid osmotic pressure gradient by the low-molecular-weight Dextran. Human studies involving small numbers of patients suggest that starches are comparable volume expanders when compared with albumin during the first 24 hours of resuscitation.

The UNC Guidelines also mentioned about the use of nonprotein colloids in thermal injury. They suggests the use of albumin if non-protein colloids are contraindicated. The relative contraindications to the use of nonprotein colloids (hetastarch, dextran, and other synthetic colloidal products) are previous hypersensitivity to the components of the solution, underlying bleeding disorders, risk of serious intracranial hemorrhage, and renal failure with either oliguria or anuria.

Langer and colleagues studied the action of hydroxyethyl starch (HES) in plasmatic clotting factor and found that cautious handling might be required in patients with clotting disturbances as well as in long-term treatment.

Diehl and colleagues also concerned that hetastarch, 6% hydroxyethyl starch solution, an artificial colloid proposed for use as a volume expander, like dextran, may adversely affect coagulation.

Data has shown that nonprotein colloid volume expanders are associated with impaired hemostasis, platelet dysfunction, and excessive bleeding. A meta-analysis of 16 trials found that there was a fourfold increase in bleeding when starches were used compared to albumin.

Yared in his research article had reviewed about the use of albumin versus non-protein colloids in fluid resuscitation and concluded that while in many situations crystalloids and non-protein colloids are acceptable alternatives to albumin, the latter remains beneficial in several specific situations. Therapy of shock with albumin as a plasma volume expander remains advantageous in patients who have renal dysfunction. Albumin is also indicated in patients with hypersensitivity to non-protein colloids or with coagulopathy, as well as in pediatric cardiac surgery, liver transplantation, plasmapheresis, and large volume paracentesis.

**CONCLUSION**

Current research in fluid resuscitation now concentrates on approaches to minimize fluid creep, including tighter control of fluid infusion.
rate. The single most important principle in using the Parkland formula, however, is that it should be used only as a guideline. The resuscitation rate and volume must be continually adjusted based on the response of the patient. Studies have been demonstrated to compare the use of crystalloids with early colloid in the first 24 hours post burn. At present, there are still wide variations in the timing of colloid resuscitation. However, use of 5% albumin in the second 24 hours seems to be an acceptable alternative.

Fluid creep is so prevalent in acute burn patients. One of the strategies to minimize it, is the earlier and more liberal use of colloids. The re-emergence of interest in use of colloids as a fluid-sparing strategy to limit ‘fluid creep’, correlates with the mechanism that colloids seem to reduce the overall volume requirements compared with the use of crystalloid alone. Based on the studies and the reports about most of the mainstream used in colloid resuscitation, we recommend the use of albumin 5% in the second 24-hours post burn, with the recommendation formula 0.3 to 0.5 mL/kg/%TBSA burn.

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