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Review Article

Intravenous Fluid Resuscitation: Breaking the Dilemma

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ABSTRACT

Intravenous fluids are core element in the resuscitation of critically ill patients, and choice & management strategies vary widely in day-to-day medical practice. With the advancement in the understanding and implementation of aggressive fluid resuscitation, has also come a greater awareness of the resultant fluid toxicity. As such, the discussion regarding intravenous solutions continue to evolve especially as it pertains to their effect on kidney and metabolic function, electrolytes, and ultimately patient outcome. This review discusses the fluid management from the perspective of resuscitative strategies, and is expected to guide clinical practitioners in fluid decision-making for common clinical scenarios encountered at acute care setups.

Key words: Albumin; Burn; Colloid; Crystalloid; Hydroxyethyl Starch; Intravenous Fluid; Normal Saline; Perioperative; Resuscitation; Sepsis; Trauma

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INTRODUCTION

Intravenous fluids are a core element in the resuscitation of critically ill patients, and choice & manage¬ment strategies vary widely in day-to-day medical practice, depending on severity, response & cause of fluid deficit, and also have been widely seen to be influenced by individual preferences. When it comes for fluid resuscitation, whether as a result of trauma, burns, major surgery, dehydration, or sepsis, crystalloids & colloids are the primary options for intravenous fluid resuscitation.

Crystalloids like saline, Ringer's Lactate, Hartmann solution, acetate solutions, or Plasma-Lyte, typically have a balanced electrolyte composition, and as they are cheap & readily available, they are most popular among clinical practitioners. On the other hands, as they have small molecule facilitating their movement into extravascular space, with overall hydrostatic effect on capillaries, increase the risk of developing edema or third space loss, which is feared to increase morbidity and total duration of hospital stay.

Colloids, like albumin, starches, dextrans, gelatin etc., on other hands, have a larger molecular weight and do not cross the endothelium, and provide volume expansion additionally by osmotic drag. But colloids are relatively expensive, and are often associated with adverse effects such as anaphylaxis, coagulopathy, and renal failure.[1]

Clinical studies have shown that colloids and crystalloids have different effects on a range of important physiological parameters.[2]

Table 1: Commonly available crystalloid and colloid formulation

Variable	0.9% Sodium Chloride	Ringer's Lactate	Plasma-Lyte A	5% Albumin	Hydroxyethyl Starch (Hespan)	Dextran 40 (in 0.9% Sodium Chloride)
Osmolality, mOsm/L	308	273	294	309	309	310
pH of solution	4.5-7	6-7.5	7.4	6.4-7.4	5.9	3.5-7
Sodium, mmol/L	154	130	140	130-160	154	154
Chloride, mmol/L	154	109	98	130-160	154	154
Potassium, mmol/L	0	4	5	≤2	0	0
Calcium, mmol/L	0	1.4	0	0	0	0
Magnesium, mmol/L	0	0	1.5	0	0	0
Lactate, mmol/L	0	28	0	0	0	0
Acetate, mmol/L	0	0	27	0	0	0
Gluconate, mmol/L		0	23	0	0	0

Whether specific properties of these fluids may translate into a survival advantage remains unclear.[3] Conflicting results from clinical trials and systematic reviews have not resolved this issue. Whatever the choice, as with other drug types, the formulation, the timing, and the dose can directly impact the outcomes of patients.[4,5] Therefore, it is clinical imperative to know their therapeutic and toxic windows to reach the optimal dose, as well as clinical decisions on type of fluid based on their side effect profile and risks and benefits.[6]

This article is a narrative review of recent evidence regarding the strategies and impact of types of intravenous fluids used in the resuscitation of patients in different clinical scenarios. The primary goal of this paper is to determine and recommend the preferred strategy and intravenous fluid for the resuscitation in different acute care setups.

COLLOIDS OR CRYSTALLOID: DEBATE OVER DECADES

Resuscitation and intravenous fluid have been a topic of frequent experimentation and discussion since the Second World War. From blood to dried plasma, and later introduction of first synthetic colloid polyvinylpyrrolidone (PVP) in late 40's, over next 40-50 years was an era were colloidal solutions were the most favored plasma expanders. It was supported by several publications as that of Shoemaker et al[7] where authors observed a greatly reduced required volume of resuscitation fluid, as well as "greater increases in hemodynamic and oxygen transport variables "after 5% albumin when compared to lactated Ringer's solution. Up to 4 times the volume of crystalloid was required to achieve the same resuscitation goals.[7]

The so called colloidal era, was soon brought in controversies, as later researches and meta-analysis showed increased risks of mortality in colloidal esp. albumin group.[8,9] And led most of its supporters switch from albumin to its cheaper alternatives like starch and gelatin products. Though these findings were later challenged by several statistically sound analysis and larger trials like SAFE, CHEST & CRISTAL, that found no mortality difference in both colloid & crystalloid groups, while increased risk of renal replacement therapy, a trend for increased bleeding, and increased blood product transfusion in the starched group,[10-14] the confusion for ideal resuscitation fluid had already taken over the medical community. These large trials lead the death of the era of starches in 2012.

In 2012, Survival Sepsis Guideline recommended use of albumin "when patients require substantial amounts of crystalloids"[15] which was later supported by ALBIOS trial which showed albumin improved mortality of septic shock patients once stability has been achieved.[16] As we stand in 2018, with advancement of dynamic hemodynamic monitoring systems and experiences from previous large trials, these recommendations didn't last longer, and currently both the Scandinavian Guidelines[17] and Survival Sepsis Campaign guidelines[18] recommend to use crystalloids instead of any colloid for resuscitation in critical illness.

RESUSCITATION IN TRAUMA PATIENTS

Intravenous fluid resuscitation in trauma patients has always been constantly reviewed and debated, resulting in frequent changes in strategies and type of fluid used which spread from crystalloids, colloids, packed red blood cells, to fresh blood and clotting factors.

Strategies

Intravenous fluid resuscitation strategy basically depends on type of trauma, which can be grossly divided to penetrating, blunt & head trauma. Restrictive fluid strategy with permitting systolic blood pressure between 60-70 mmHg is often a preferred choice in penetrating injuries, particularly of the thoracic and abdominal region, until the patient can be taken to the operating theater. Whereas a slighter higher systolic blood pressure of 80-90 mmHg is permitted with slower infusions in context of blunt injuries.19 This restrictive strategy is thought to minimize intra-abdominal

Table 2: Intravenous Fluid response assessment

Systolic Blood Pressure Goals
Penetrating 50-70 mmHg
Blunt 80-90 mmHg
+/- TBI 100-110 mmHg (MAP > 70)
Lactate clearance with target < 2.0
Base Deficit (BD) < -5
Improving pH to > 7.3
Normothermia or at least T > 35.5oC

Responder = achieves set target/goals
Non-responder = fails to reach set target/goals
Transient responder = temporarily reaches set target/goals but then decompensate later

Source: Wise R, Faurie M, Malbrain MLNG, Hodgson E. Strategies for Intravenous Fluid Resuscitation in Trauma Patients. World J Surg. 2017;41(5):1170–83.

bleeding while maintaining adequate organ perfusion and reducing the risk of intra-abdominal hypertension and complications. Once hemorrhage has been controlled in theater and blood products are available, higher blood pressure values may be targeted.[20]

The exception to the above is the poly-trauma patient (blunt or penetrating) with traumatic brain injury (TBI). In order to preserve adequate cerebral perfusion pressure and prevent secondary brain injury, one needs to target a mean arterial pressure (MAP) of greater than 80 mmHg (a cerebral perfusion pressure of approximately 60 mmHg).[19] Though whatever be the nature of trauma, one should always remembered that clinical scenarios are often overlapped and complicated, and these strategies & blood pressure goals should be individualized according to patient's physiology, co-morbidities and physiological compensation to shock during the time of resuscitation.[20]

Choice of Fluid

As discussed earlier, over decades of trials & meta-analysis, crystalloids have been shown to have preference in resuscitation which is supported by availability & relative cost effectiveness. Though some trials like CRISTAL[14] showed colloids to have 90 days mortality benefit (30.7% dead in the colloid group vs. 34.7% in the crystalloid group) and better results at staying off the ventilator and off vasopressors, overall quality of research and relationship with cofounding characters need further researches.
When considering synthetic colloids, risk-adjusted analyses by Hilbert-Carius et al.[21] revealed that patients receiving >1,000 ml synthetic colloids experienced an increase of renal failure and renal replacement therapy rates (OR 1.42 and 1.32, respectively, both $p \leq 0.006$). Any synthetic colloid use was associated with an increased risk of multiple organ failure ($p < 0.001$), but there was no effect on hospital mortality ($p= 0.594$). Despite the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) have recommend Hydroxyethyl Starch (HES) dose of 30 ml/kg once in 24 hours, the data from their analysis suggested that synthetic colloid resuscitation provides no beneficial effects and might be harmful in patients with severe trauma.[21]

Balanced vs. 0.9% Saline

Despite 0.9% Sodium Chloride solution being most widely used and popular among resuscitative fluids, the meta-analysis by Krajewski et al.[22] showing a significant association between high chloride content in resuscitative fluid and acute kidney injury, blood transfusion volume and mechanical ventilation time, brought the debate – whether a more balanced salt solutions (e.g., Ringer's lactate, Hartmann's solution, Plasma-Lyte) could yield better results.

Balanced salt solutions closely resemble human plasma and thus have a lower sodium and chloride content than 0.9% saline with the addition of a buffer such as acetate or lactate. These fluids have minimal effects on pH but are hypotonic, so can exacerbate edema, particularly cerebral edema in the injured brain. In addition, when using Ringer's lactate solution, consideration should be given to the potential interaction between citrate found in stored blood and bicarbonate.[23]

In summary, on grounds of currently available resources & researchers, saline is preferable in brain injured, hyponatremic and patients with metabolic alkalosis; whereas balanced solutions are preferable in patients who are already acidotic & other clinical case scenarios.

Volume of Resuscitative fluid

The physiological impact of the volume of fluid infused may be as, or even more important than the type selected.[24-28] Excessive fluid results in a dilutional coagulopathy and diffuse tissue edema. This negatively impacts organ function at both a macroscopic and cellular level by increasing the distance over which electrolytes, elements and oxygen have to move.[29] The consequence is worsening renal, hepatic and cardiac function as well as increasing volume of extra vascular lung water that worsens ventilation–perfusion mismatch. Abdominal hypertension/ compartment syndrome may progress to a poly-compartment syndrome.[25-28] Therefore, until such time as blood and blood products are available, clear fluid resuscitation should be limited to only that which is necessary to maintain adequate organ perfusion.

SPECIAL GROUPS

Pediatrics: Children differ from adults in having a larger circulating blood volume (80 ml/kg in a term neonate) that decreases with age to the adult level of 70 ml/kg.[30] While the principles of goal-directed therapy apply equally well to children as to adults. Initial resuscitation should be with 20 ml/kg of balanced crystalloid, and with similar adverse effects like dilutional coagulopathy, anemia and edema (including ileus, abdominal compartment syndrome and ARDS), the volume of clear fluid should not exceed 40 ml/kg.[31]

Administration of blood and blood products (platelets and plasma) should be considered depending on the response to the initial 20 ml/kg crystalloid bolus and the severity of injury. Due to the small volumes required, many pediatricians use human colloids such as plasma or albumin for intravascular volume replacement in preference to synthetic clear fluids.[32]

Elderly: Cardiovascular changes of aging include stiffening of the arterial circulation and loss of compliance of the left ventricle. The elderly thus tolerate hypo- and hypervolemia poorly. Volume loss reduces preload resulting in ventricular under-filling and a disproportionate drop in cardiac output. Over-hydration is as dangerous due to the lack of ventricular compliance predisposing to the development of edema, particularly pulmonary edema.[33]
Considering above factors, clear fluid administration should initially be limited to 20 ml/kg with early consideration given to the administration of blood and blood products. Careful re-evaluation and vigilant monitoring should to performed to determine if further fluid administration is required; particularly if underlying heart disease is suspected. Due to the likelihood of underlying coronary and cerebral artery disease in the elderly, consideration should be given to maintaining hemoglobin levels above 9 g/dl and mean arterial pressure above 70 mmHg, particularly if the patient's comorbidities are unknown.[33]

ASSESSMENT OF VOLUME RESPONSE

Response to fluid administration and determining the need for further fluid administration is necessary, especially when it is associated with significant adverse effects related to volume overload, as discussed earlier.

The response to intravenous fluid can be assessed using physiological markers like improvement of heart rate, blood pressure, lactate clearance, normalization of base deficit etc, as well as by more advance dynamic hemodynamic monitoring techniques like pulse pressure variation (PPV), stroke volume variation (SVV) etc. Depending on these parameters, patients can be categorized to Responders, Transient-Responders or Non-Responders, and fluid resuscitation tailored, as depicted in table 2.[20]

RESUSCITATION IN BURN PATIENT

Shock in burn patients has been associated with its severity, and is initially triggered by systemic inflammatory response and later by increased vascular permeability, leading to significant third space loss. Mainstay of treatment, in such patients is providing supportive care with fluid resuscitation until vascular permeability is restored and interstitial fluid losses are minimized.[34]

Unlike other resuscitation strategies e.g. in trauma patients, resuscitation in burn patient is bit challenging, because with over-resuscitation conversion of partial-thickness burns to full thickness, pulmonary oedema and abdominal compartment syndromes, are more frequent because of accompanying inflammatory cascades. Hence resuscitation in burn patients requires continuously adjustment to prevent over-resuscitation and under-resuscitation.[35]

Strategy

Multiple formulas have been advocated so far, of which the Parkland formula is the most popular. Using this formula, fluid needs are estimated at 4 mL/kg/% burn for the first 24 hours, with half of the total volume given within the first 8 hours.

As discussed earlier, with continued resuscitation efforts, the rate and type of fluid, needs to be continuously reviewed to prevent under-resuscitation or over-resuscitation and associated complications, in burn patients. It can be guided by conventional parameters like heart rate, blood pressure, urine output, base deficit etc or more recent dynamic haemodynamics & volume status assessment tools like stroke volume variance, pulse wave variance analysis etc.

Choice of Fluid

There have been several researches supporting superiority of colloids especially albumin, promoting its continued use in management of burn patients, over decades. One of the similar studies, albumin was linked with decreased mortality when controlling for age, burn size, and inhalational injury.[36] In another retrospective study specific to patients with large burns, albumin use was demonstrated to decrease the incidence of extremity compartment syndrome and renal failure.[37] Similarly, a most recent meta-analysis of albumin use in acute burn resuscitation found that its use was associated with decreased mortality and decreased incidence of compartment syndrome.[38]

However, the evidence against use of colloids is equally plentiful, in burn patients. Colloid use has been associated with increased lung water after finishing resuscitation.[39] And colloids especially albumin & FFP can cause transfusion-associated lung injury and allergic and anaphylactic reactions.

For early resuscitative goal, Cochrane systematic reviews concluded that in resuscitation of critically ill patients, there is no improvement in mortality when using colloids over crystalloids alone.[2] For the similar reasons, as stated in trauma section, supported by researches in critically ill and trauma patients with hypovolaemic shock, crystalloids are favourable in early resuscitation for burn patients as well. Though there is no concensus statement regarding the most appropriate choice among crystalloids, balanced solutions especially Ringer's Lactate, have had preferences over others because of its physiological effect & proven track record.

In theory, the capillary beds in non-burned tissue return to baseline levels of permeability at 5 to 8 hours after initial thermal injury.[40] Hence after this period, resuscitation with colloids, such as albumin or fresh frozen plasma (FFP), could provide circulating intravascular volume and lessen fluid needs.[41,42] Decreased fluid volumes during initial resuscitation would lead to less global tissue oedema and therefore decreased risks of compartment syndromes or other sequel of over-resuscitation.

In summary, given that colloids are more expensive and may have drawbacks when compared with balanced crystalloid solutions alone, the clinician should consider balanced crystalloid like ringer's lactate during initial resuscitation followed by judicious colloid (albumin or FFP) use to lessen total resuscitative fluid requirement, hence preventing associated complications of volume overload. Consideration should be made for colloids especially when handling patients with fluid-sensitive comorbidities, such as in chronic renal failure or heart failure.[34]

RESUSCITATION IN PATIENT WITH SEPSIS & SEPTIC SHOCK

Early effective fluid resuscitation is crucial for the stabilization of sepsis-induced tissue hypoperfusion or septic shock. Given the urgent nature of this medical emergency, initial fluid resuscitation should begin immediately upon recognizing a patient with sepsis and/or hypotension and elevated lactate.[18]

Unlike trauma and burn, shock in sepsis is majorly a sequel of systemic inflammatory response, and of redistributive/ vasodilatory property, making source control equally important as intravenous fluid, and it may often require vasopressors, in course of management.

Strategy

Current guidelines for the management of patients with sepsis and septic shock recommend to begin rapid administration of 30ml/kg crystalloid for hypotension or lactate $\geq$ 4 mmol/L, and to start vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP $\geq$ 65 mmHg.[18] Although little literature includes controlled data to support this volume of fluid, recent interventional studies have described this as usual practice in the early stages of resuscitation, and observational evidence supports the practice.[43,44] The average volume of fluid pre-randomization given in the PROCESS and ARISE trials was approximately 30 mL/kg, and approximately 2 L in the PROMISE trial.[45–47] Many patients will require more fluid than this, and for this group it is advisable that further fluid be given in accordance with functional hemodynamic measurements.[48]

Choice of Fluid

The absence of any clear benefit following the administration of colloid compared with crystalloid solutions in the combined subgroups of sepsis, in conjunction with the expense of albumin, supports a strong recommendation for the use of crystalloid solutions in the initial resuscitation of patients with sepsis and septic shock.[18] This recommendation from Surviving Sepsis Campaign, is backed by several trials and meta-analysis which found no mortality benefit of albumin over crystalloids, as a resuscitative fluid, in patients with sepsis & septic shock.[49-52]

Cristalloid: With the similar physiological benefits as described in trauma section, balanced crystalloids appear to be a superior alternative to saline for resuscitation of patients with sepsis. Hence, balanced crystalloids may improve patient-centered outcomes and should be considered as an alternative to normal saline, if available.[53]

Colloid: There is strong evidence that suggests semi-synthetic colloids, like HES, decrease survival and were associated with increased risk of renal renal replacement therapy, a trend for increased bleeding, and increased blood product transfusion, hence should be avoided.[12,13] The role of albumin in the resuscitation of patients with sepsis is uncertain, findings from studies similar to ALBIOS trial, which showed benefits in septic shock patient once hemodynamic stability is achieved[51], suggest likely additional benefit of albumin if used in addition to crystalloids for initial resuscitation and subsequent volume expansion when patients require substantial amounts of crystalloids, and when resuscitation is failing.

In summary, balanced crystalloids should be considered as a preferable alternative to 0.9% Saline, if available, and colloids especially albumin be reserved for septic patients requiring large amounts of crystalloids. Additionally, it is strongly advised to avoid HES solutions patients with sepsis and septic shock.

RESUSCITATION DURING PERIOPERATIVE PERIOD

Perioperative fluid management is a key component in the care of the surgical patient. It is an area that has seen significant changes and developments, however there remains a wide disparity in practice between clinicians.[54]

Historically, patients received large volumes of intravenous fluids perioperatively, which was later challenged, as association between perioperative morbidity and volume of fluid therapy administrated was seen. A U-shaped curve of association with increased mortality associated with very high or very low volumes of fluid administration was described.[55] Following which the concept of goal directed therapy was introduced.

Strategy

Goal directed therapy (GDT), in summary targets fluid therapy with aim of optimizing patient's cardiac function and oxygen delivery. Guided by hemodynamic monitoring, it avoids risks of over-resuscitation and its associated complications. Hence it has been promoted in perioperative period in patients requiring fluid resuscitation.

Despite heterogeneity in trial quality and design, GDT was found beneficial in all high-risk patients undergoing major surgery. Though mortality benefit of GDT was confined to the subgroup of patients at extremely high risk of death, the reduction of complication rates was seen across all subgroups of GDT patients.[56]

With current disparity, and supported by various non-inferiority studies especially in non-GDT group of low-moderate risk surgeries, majority supports the implementation of a two-step GDT plan which is to begin immediately after induction of anesthesia. First, determine if the patient requires hemodynamic support or augmentation of cardiovascular function. Second, if the need is apparent and the patient is fluid responsive, fluid bolus therapy should be considered and guided by continual, and if available continuous, assessment of fluid responsiveness as described below.[54]

FLUID CHALLENGE & FLUID RESPONSIVENESS AND BOLD

It is important that the assessment of fluid responsiveness is used as part of a complete assessment of a patient's clinical condition and fluid status to determine whether they need or it is appropriate for them to receive further intravenous fluids.[54]
The assessment of fluid responsiveness relies on the administration of a fluid challenge. Aya et al. support a fluid challenge of 4 ml/kg to differentiate responders from non-responders.[57]

Choice of Fluid

Historically, colloids were frequently used; it was believed that as colloids were more likely to remain intravascular than crystalloids, and greater haemodynamic stability could be achieved with lower volumes.[58] Several large studies have however refuted this. With consistent evidence of increased acute kidney injury, need for renal replacement therapy and 90 day mortality in patients receiving colloids, particularly starches, compared to patients receiving crystalloids, crystalloids now form the mainstay of treatment.[59] A number of the studies on the use of colloids have been performed in critically ill patients. However, a recent meta-analysis included surgical patients and reported similar results.[2] Given these findings, the safety profile of starches for perioperative use has been questioned, and it is the advisable that their use should be avoided, with crystalloids forming the mainstay of treatment.[58]

Which crystalloid to use has also been investigated, generally either 0.9% saline or a balanced solution such as Hartmann's is used. 0.9% saline has a chloride concentration of 154 mmol which is significantly higher than serum chloride. It is well recognised that its use can lead to a hyperchloremic acidosis. Post-operative hyperchloremia has been linked with increased post-operative complications, such as acute kidney injury and increased 30-day mortality, although causation has not been proved.[60] Balanced solutions, which include Hartmann's solution or Plasma-Lyte , are considered more physiological and generally preferred for perioperative fluid management.[58,61]

In summary, crystalloid solutions preferable balanced solutions should be first choice for routine surgery of short duration. However, in major surgery, the use of a goal-directed fluid regimen containing colloid with balanced-salt solutions should be preferred.[54] While starch solution avoided at all cost, as it is associated with increased risk of renal renal replacement therapy, a trend for increased bleeding, and increased blood product transfusion.

CONTINUOUS MONITORING FOR RESPONSIVENESS

As hinted earlier, continuous monitoring and tailoring of the intravenous fluid therapy is an essential part of any resuscitative strategy. Assessment of responsiveness of rapid fluid administration through markers like pulse pressure variation (PPV), stroke volume variation (SVV), passive leg raise (PLR) tests, prevent fluid overload & its associated complications.(20) Whereas in certain circumstances where patients remain fluid responsive, curtailment of ongoing fluid resuscitation may be necessary if the tolerance to further intravenous fluid is deemed detrimental to physiological processes (for example, abrupt increase in extravascular lung water; worsening intra-abdominal pressure or abdominal compartment syndrome; difficult ventilation).[62] Alternative strategies should be considered including inotropic support guided by cardiac output monitoring, alternative fluid strategies, and planning for hemodialysis with net ultrafiltration.[20]

CONCLUSIONS

Current literatures support use of balanced crystalloid solutions as first line resuscitative fluid for almost all critical care scenarios, while colloid solutions are reserved for specific conditions with high fluid demand or when excessive interstitial volume overload is feared. And among colloids, starch solution like HES should be avoided due to high risks associated with its use, in nearly every resuscitative scenario discussed.

Meanwhile, clinical practitioners should keep in mind that intravenous fluids are not less than drugs, and hence should be treated as prescription medications. The appropriate fluid type and dose should be carefully chosen for each clinical scenario, and tailored to individual patients, and its response, evident through continuous monitoring of dynamic markers of volume status.

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