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SYSTEMATIC REVIEWS

Plasma-Lyte 148: A clinical review

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Abstract

AIM

To outline the physiochemical properties and specific clinical uses of Plasma-Lyte 148 as choice of solution for fluid intervention in critical illness, surgery and perioperative medicine.

METHODS

We performed an electronic literature search from Medline and PubMed (*via* Ovid), anesthesia and pharmacology textbooks, and online sources including studies that compared Plasma-Lyte 148 to other crystalloid solutions. The following keywords were used: "surgery", "anaesthesia", "anesthesia", "anesthesiology", "anaesthesiology", "fluids", "fluid therapy", "crystalloid", "saline", "plasma-Lyte", "plasmalyte", "hartmann's", "ringers" "acetate", "gluconate", "malate", "lactate". All relevant articles were accessed in full. We summarized the data and reported the data in tables and text.

RESULTS

We retrieved 104 articles relevant to the choice of Plasma-Lyte 148 for fluid intervention in critical illness, surgery and perioperative medicine. We analyzed the data and reported the results in tables and text.

CONCLUSION

Plasma-Lyte 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition

that closely reflects human plasma. Emerging data supports the use of buffered crystalloid solutions in preference to saline in improving physicochemical outcomes. Further large randomized controlled trials assessing the comparative effectiveness of Plasma-Lyte 148 and other crystalloid solutions in measuring clinically important outcomes such as morbidity and mortality are needed.

Key words: Surgery; Anesthesia; Fluid therapy; Crystalloids; Saline; Plasma-Lyte; Hartmann's; Ringers; Acetate; Gluconate; Lactate

Core tip: Plasma-Lyte 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition that closely reflects human plasma. It is physiologically different to the commonly available crystalloids solutions such as Hartmann's solution and sodium chloride (0.9%). Before using any crystalloid solution as fluid therapy, clinicians should have a fundamental understanding of each fluids specific physiological properties.

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INTRODUCTION

The use of intravenous (*IV*) fluids for maintenance therapy and resuscitation in anesthesia and critical care medicine is universal. There is marked variation in perioperative fluid selection that is generally decided by institution and clinician preference. Such practice variation is related to the paucity of prospective evidence evaluating the comparative safety and efficacy of available crystalloid solutions for both fluid resuscitation and maintenance therapy in the perioperative setting. Compared to colloids, crystalloids are often the preferred solution for replacement or maintenance fluid therapy as they are relatively cheap, commonly available, easily transportable and storable with a good shelf life, and have no allergy risk. In addition, crystalloids are easy to manufacture, require no special compatibility testing, are widely available and accessible even in developing countries, and can be freely given to patients with religious objections to blood or blood related products. Currently, sodium chloride 0.9%, commonly referred to as normal saline 0.9% (NS), Ringer's Lactate and Hartmann's solution are commonly available crystalloid solutions worldwide. However, their electrolyte composition is significantly different from that of plasma[1]. In contrast, Plasma-Lyte 148 (PL 148) has physiochemical properties similar to plasma, however PL 148 has yet to be the subject of a detailed clinical review. Therefore, we present a comprehensive review of PL 148, comparing its physiochemical properties to other commonly available crystalloids solutions and evaluating its utility as a buffered fluid solution. We also discuss the role of PL 148 solution in critical care medicine and anesthesia.

MATERIALS AND METHODS

We performed an electronic literature search from Medline and PubMed (*via* Ovid), anesthesia and pharmacology textbooks, and online sources. The following keywords were used: "surgery", "anaesthesia", "anesthesia", "anesthesiology", "anaesthesiology", "fluids", "fluid therapy", "crystalloid", "saline", "Plasma-Lyte", "plasmalyte", "hartmann's", "ringers" "acetate", "gluconate", "malate", "lactate". Only studies that compared PL 148 to other crystalloid solutions were included. Articles in the English language with human and animal studies were considered. Date restrictions were not applied. The last electronic literature update was in December 2015. In total, after appropriate screening against the inclusion criteria, we retrieved 557 references or full-text journal articles for analysis and critical review. Three authors conducted the search and data extraction. Two authors analyzed the results. Including online journal articles and textbooks, 104 articles were included this review.

RESULTS

Description of product

PL 148, also known as Plasma-Lyte A, is a sterile isotonic non-pyrogenic IV crystalloid solution used in clinical medicine to provide water, electrolytes and calories to patients. PL 148 is a trade mark of Baxter International Inc. First patented in 1982, it is available in 1000 mL and 500 mL Viaflex containers and has been commercially available for peri-operative fluid intervention for over 25 years in the United States, Australasia and the United Kingdom. The electrolyte composition of PL 148 more closely reflects the constituents of human plasma compared with both Hartmann's Solution and NS, and is hence considered a more "physiological" solution. It is commonly used as both a resuscitation and maintenance fluid in the critical care setting and for perioperative fluid intervention in elective and emergency surgery.

Each 1000 mL of PL 148 contains 5.26 g sodium chloride, 370 mg potassium chloride, 300 mg magnesium chloride, 3.68 g and 5.02 g of sodium acetate and sodium gluconate respectively; this equates to 140 mmol/L sodium, 5 mmol/L potassium, 1.5 mmol/L magnesium, 98 mmol/L chloride, and 27 mmol/L and 23 mmol/L of acetate and gluconate, respectively. The physiochemical properties of PL 148 compared to plasma and other commonly available crystalloid solutions are summarized

Table 1 Characteristics of common crystalloid solutions compared to human plasma

	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Acetate (mmol/L)	Gluconate (mmol/L)	Lactate (mmol/L)	Malate (mmol/L)	eSID (mEq/L)	Theoretical osmolarity (mOsmol/kg)	Actual or measured [1]osmolality (mOsmol/kg)	pH
Plasma	136-145	3.5-5.0	0.8-1.0	2.2-2.6	98-106	Nil	Nil	Nil	Nil	42	291	287	7.35-7.45
Sodium chloride (0.9%)	154	Nil	Nil	Nil	154	Nil	Nil	Nil	Nil	0	308	286	4.5-7
Compound sodium Lactate (lactate buffered)	129	5	Nil	2	109	Nil	Nil	29	Nil	29	28	278	5-7
Ringer's lactate (lactate buffered)	130	4	Nil	3	109	Nil	Nil	28	Nil	27	278	256	5-7
Ionosteril® (acetate buffered solution)	137	4	1.25	1.65	110	36.8	Nil	Nil	Nil	36.8	291	20	6.9-7.9
Sterofundin ISO® (acetate and malate buffered)	145	4	1	2.5	127	24	Nil	Nil	5	25.5	309	Not stated	5.1-5.9
Plasma-Lyte 148® (acetate and gluconate buffered)	140	5	1.5	Nil	98-106	27	23	Nil	Nil	50	295	271[2]	7.4[3]

[1]Freezing point depression; [2]Australian and New Zealand formulation; however approximate osmolality may vary depending on country of manufacture; [3]Australian and New Zealand formulation; however pH ranges from 6.5 to 8.0 depending on country of manufacture. Plasma-Lyte 148 manufactured by Baxter Healthcare, Toongabie, NSW, Australia; Ringer's Lactate manufactured by Baxter Healthcare, Deerfield, IL, United States; Hartmann's solution manufactured by Baxter Healthcare, Toongabie, NSW, Australia; Ionosteril manufactured by Fresenius Medical Care, Schweinfurt, Germany; Sterofundin ISO manufactured by B. Braun Melsungen AG, Melsungen, Germany.

in Table 1. Unlike Hartmann's solution, which contains calcium, PL 148 is calcium free and therefore compatible with blood and blood components. PL 148 contains no antimicrobial agents. The caloric content is approximately 66 kilojoules/L or 16 kcal/L. The numeric "148" is a derivative of the sum of each of PL 148's cationic concentrations, *i.e.*, 140 mEq (sodium) plus 5 mEq (potassium) plus 3 mEq (magnesium), which equates to a sum total of "148 mEq". The formulation "PL 148 (approximate pH 7.4)" is available in Australia and New Zealand. The formulation is approved by the Australian Therapeutics Goods Administration and registered in both Australia (AUST 231424 and 48512) and Medsafe (New Zealand). The pH of PL 148 is adjusted with sodium hydroxide and reported as approximately 7.4, however depending on country of manufacture, the pH ranges from 6.5 to 8.0. PL 148 is supplied in VIAFLEX™ plastic bag containers produced from a uniquely formulated polyvinyl chloride. VIAFLEX is a trademark of Baxter International Inc. Safety of the polyvinyl chloride has been confirmed in animal and tissue culture toxicology studies.

DISCUSSION

Contraindications and precautions

There are no published cases in the medical literature of PL 148 hypersensitivity reactions, however anaphylactic and hypersensitivity infusion reactions have been reported[2]. As the PL 148 bag is an adaptable or flexible plastic container, it should not be connected in series with other fluid containers due to the risks of air embolism. Pressure infuser bags to increase flow rates should be used very cautiously with any of the PL 148 containers, as any residual air in the container that has not been evacuated prior to administration, can result air embolism. Similarly, the use of open vented IV administration sets can also result in air embolism, and these should not be used with the PL 148 flexible container.

Compatibility with other IV medications

The physical compatibility of PL 148 with medications commonly used in the operating theatre and critical care settings has been investigated[3]. PL 148 was

tested with 87 drugs for physical compatibility immediately on mixing, 1 h and 4 h after mixing. Y-site compatibility was determined by visual examination performed with laboratory light. Turbidity was measured with high-intensity light using a portable turbidimeter. On mixing, visual appearance changes occurred with amiodarone, cyclosporine, propofol and mycophenolate. An increase in turbidity was observed with pantoprazole and phenytoin, amiodarone, cyclosporine, propofol and mycophenolate.

Drug interactions

Similar to all crystalloid solutions, PL 148 should be used cautiously in patients on corticosteroids due to additive risks of sodium and fluid retention. More specific to PL 148, due to its alkalinizing effects, the renal elimination of acidic drugs such as aspirin and barbiturates, or drugs such as lithium, may increase[2]. The renal elimination of alkaline drugs such as quinidine, or dextroamphetamine (dexamphetamine) and sympathomimetics (*e.g.*, ephedrine) may be decreased. At present there is insufficient evidence for any dose adjustment with any of the stated interacting drugs.

Drug and laboratory test interactions

As gluconate plays a role in the galactomannan antigenicity of PL 148, patients receiving PL 148 may test positive for the galactomannan antigen. Previous studies have reported that patients and healthy volunteers receiving PL 148 have demonstrated a false-positive circulating galactomannan test lasting for up to 24 h[4-7]. Galactomannan antigen is a biomarker for pulmonary aspergillosis in immunocompromised patients. Positive test results in patients receiving PL 148 should therefore be interpreted cautiously and the galactomannan antigen should be confirmed by other diagnostic methods[4]. More recently however, Spriet *et al*[8] tested 33 distinct batches of PL 148 and reported that with contemporary sophisticated manufacturing processes, PL 148 does not result in false-positive galactomannan test results.

Carcinogenesis, pregnancy and geriatric patients

There are no studies of PL 148 that have evaluated its carcinogenic and mutagenic potential. It is unknown if PL 148 has any effects on fertility. In the United States, PL 148 is classed as "Category C" in pregnancy. No "category" is stated in the Australian Product Information for PL 148. Drugs in "Category C" may cause harmful, but reversible effects to the fetus or neonate, however do not result in deformity or malformation. The Australian categorization system of medicines for use in pregnancy differs from the Food and Drug Administration categorization in the United States and does not follow a hierarchical structure. To date, there are no animal reproduction studies of PL 148 and it is not known if PL 148 causes foetal adverse effects when administered during pregnancy, or whether PL 148 affects reproduction capacity. There is no evidence to suggest that PL 148 is excreted in breast milk. There is insufficient information to determine if elderly patients respond differently from younger subjects. In general, dose selection of PL 148 in the elderly should take into consideration cardiac, renal, and hepatic function, together with pre-existing comorbidities and pharmacological therapy.

Physiological properties of PL 148

PL148 is marketed as a "physiological" and "balanced" fluid, because its composition closely reflects that of plasma. Its physiochemical properties are however different from the commonly used crystalloids: NS and Hartmann's solution. Outlined below are the key differences between PL 148 and these commonly available crystalloid solutions.

Osmolality: Normal plasma osmolality is 280-296 mOsmol/kg. PL 148 is an isotonic solution with an approximate osmolality of 271 mOsmol/kg (current formulation in Australia and New Zealand), as determined by an osmometer using the technique of freezing-point depression. In other countries, the stated osmolality is approximately 291 mOsmol/kg. Osmolarity is the measure of the solute concentration, or the number of osmoles of solute particles per unit volume of solution. The osmotic pressure of a solution determines how a solvent will diffuse across a semipermeable membrane (osmosis) that separates two solutions of different osmotic concentrations. The osmotic activity of IV fluids is best described by the calculated *in vivo* osmolality (mOsmol/kg) of that solution[9]. Tonicity on the other hand, is a measure of the effective osmotic pressure gradient of two different solutions that are separated by a semipermeable membrane. Therefore, tonicity can be described as the "relative concentration" of solutions, which in turn, determine the direction and degree of diffusion of that solution. The terminology is distinctive; osmolarity is the total concentration of diffusible and non-diffusible solutes, whereas tonicity takes into account the total concentration of only non-diffusible solutes.

PL 148 is considered a "balanced" fluid and isotonic with plasma, because it has a calculated *in vivo* osmolality within the normal physiological range of 270 to 290 mOsmol/kg[10]. Interestingly, NS is considered "hypertonic" with an *in-vitro* osmolality of 308 mOsmol/kg (154 mOsmol/kg Na^+, 154 mOsmol/kg Cl^-). However, as its electrolyte components are only partly active (osmotic coefficient of 0.926[9]), NS is "isotonic" (calculated *in-vivo* osmolality of 287 mOsmol/kg[11]). In contrast to both PL 148 and NS, Hartmann's solution is relatively "hypotonic" with an *in-vivo* osmolality of 254 mOsmol/kg. Fluids that are hypotonic relative to plasma, can result in retention of free water and consequent hyponatremia, effects frequently compounded by the release of anti-diuretic hormone, which is stimulated with critical illness,

anesthesia, and surgical stress[12]. Hypotonic fluids should be used extremely cautiously, if at all, in patients with fluid overload states, hyponatremia, critical illness, or in the setting of raised intracranial pressure. Failure to excrete this water load can cause postoperative fluid balances excess, weight gain, and resulting tissue edema and cellular dysfunction[13].

Chloride concentration: Normal plasma concentration of chloride ranges between 98 and 106 mmol/L. PL 148 contains a physiological amount of chloride (98 mmol/L), whilst Hartmann's solution is slightly hyperchloremic relative to plasma (109 mmol/L). In contrast, NS contains supra-physiological concentrations of chloride (154 mmol/L), with accumulating data and expert opinion supporting the view that large volumes of NS cause a normal anion gap hyperchloremic metabolic acidosis[14]. Even the infusion of IV NS over a few hours has been shown to cause a metabolic acidosis *via* this mechanism[15-19]. Whilst the development of acidosis may result in impaired cardiac contractility, arrhythmias, pulmonary hypertension, renal and splanchnic vasoconstriction and impaired coagulation[10], the physiological benefits of an acidemia include improved oxygen delivery *via* the Bohr effects and acidemic protection against hypoxic stress[10,20-22].

Hyperchloremia has recently been linked to adverse clinical outcomes in several animal and human studies. McCluskey *et al*[23] reviewed the datasets of 22851 surgical patients undergoing non-cardiac surgery with normal chloride concentration and kidney function. Postoperative hyperchloremia (defined as plasma chloride > 110 mmol/L) occurred in 22% of patients. Hyperchloremia was associated with adverse renal outcomes and 30-d mortality. Similarly, the adoption of a chloride-restriction protocol in a university hospital critical care unit was also associated with a decrease in AKI and renal replacement therapy[24]. Finally, in a trial examining outcomes in patients receiving major abdominal surgery who were administered PL 148 or NS for routine perioperative fluid intervention, there was an increased risk of major adverse events, particularly infection and acute kidney injury, among patients who received NS[25]. It was unclear if the higher incidence of AKI was due to hyperchloremia or other confounding factors. The suggested mechanisms of hyperchloremic induced kidney injury include inability of the proximal tubules to reabsorb chloride, increasing transport of chloride to the distal tubule, thereby decreasing glomerular filtration[26-28], hyperchloremic induced thromboxane[29], and inflammatory mediator and cytokine release[30].

In an animal model evaluating the effects of fluid resuscitation with NS *vs* PL 148 on acute kidney injury in sepsis, NS resuscitation resulted in significant hyperchloremia and acidemia[30]. Acute kidney injury severity was increased with NS compared with PL 148 resuscitation, and 24-h survival favored PL 148 resuscitation. In an animal model of hemorrhagic shock, resuscitation with PL 148 resulted in a more effective restoration of blood pressure, and improved biochemical profiles when compared to NS[31]. This study also showed that resuscitation with PL 148 improved renal oxygen consumption. Chowdhury *et al*[32] performed a clinical trial examining kidney blood flow and cortical perfusion in healthy participants who were given 2000 mL of NS or PL 148. Participants receiving NS had reduced renal blood flow and cortical perfusion. Furthermore, in another volunteer study participants received a fast infusion of 2000 mL of NS and renal excretion took more than 2 d[33]. This was further supported by a study by Stenvinkel *et al*[34] where healthy volunteers who received 2000 mL of NS over 2 h were noted to have a decrease in their eGFR by 10%. Recently, in a blinded, cluster randomised, double-crossover trial the renal effects of PL 148 and NS were investigated in patients admitted to four ICUs. In this trial, 1152 patients received PL 148 and 1110 patients received NS[35]. No substantial difference in AKI between the groups was reported. Adequately powered clinical trials are eagerly awaited to evaluate the efficacy of PL 148 and NS in high-risk patients that report clinically important outcomes such as major morbidity and mortality. Current research programs are underway with details on the trial designs already published[36]. There is still ongoing debate as to whether NS should be replaced with balanced crystalloids for both fluid maintenance and resuscitation to minimise acute kidney injury[37,38].

Other electrolytes: Similar to Hartmann's solution, PL 148 has a potassium content of 5 mmol/L; PL 148 should be used cautiously in patients receiving ACE inhibitors or angiotensin II receptor antagonists, calcineurin inhibitors, *e.g.*, tacrolimus, and the immunosuppressant cyclosporine, due to increase the risk of hyperkalemia. Similarly, PL 148 should be used cautiously in patients with hyperkalemia or who are predisposed to severe hyperkalemia, *e.g.*, rhabdomyolysis, severe burns, renal failure, and adrenocortical insufficiency. Unlike Hartmann's solution or Ringer's lactate, PL 148 contains 1.5 mmol/L magnesium and should be used cautiously in patients with hypermagnesemia or who are at risk of hypermagnesemia. Further, in patients receiving PL 148, magnesium levels should be checked before additional magnesium is administered. However, PL 148 is not indicated for the treatment of hypomagnesemia. Hartmann's solution contains calcium and should be used cautiously with blood or blood derivatives, due to the potential risks of precipitation and clot formation[39]. In contrast, PL 148 is calcium free and completely compatible with blood or blood components. The mixing of fluids containing calcium and magnesium with drug salts of phosphates, carbonates, tartrates or sulfates should also be avoided due to risks of forming insoluble calcium or magnesium salts. Mixing calcium-containing solutions, *e.g.*, Hartmann's with ceftriaxone can cause the formation of insoluble ceftriaxone calcium salts[40].

Strong ion difference: An important physicochemical

property of PL 148 compared to other crystalloid solutions is its ability to increase pH in patients with a pre-existing metabolic acidosis. Experimental evidence has shown that the optimal effective *in-vivo* strong ion difference (SID) for an IV fluid not to influence blood pH should be approximately 24 mEq/L[41,42]. Saline 0.9%, with its equal concentrations of sodium and chloride, has a SID of zero. It follows that infusion of NS will significantly reduce the SID of plasma, thus causing a metabolic acidosis. Hartmann's solution is considered to be a "balanced" solution compared to NS, with an effective *in-vivo* SID of 29 mEq/L. PL 148 has a SID of 50, which is the reason it is considered an "alkalinizing" solution. As PL 148 is an alkalinizing solution, its administration may increase plasma pH, which can decrease ionized calcium concentrations. Whilst PL 148 may correct an underlying metabolic acidosis, it should be administered cautiously, if at all, to patients with alkalosis.

Inorganic and metabolic anions in Plasma-Lyte 148

Acetate: Normal physiological levels of acetate are 0.06-0.2 mmol/L in plasma. The acetate concentration in PL 148 is 27 mmol/L. Acetate is no longer used as a hemodialysis buffer in modern dialysis treatments. Although initial studies showed that acetate based solutions were almost as effective as bicarbonate in maintaining acid base homeostasis in patients with cholera[43,44], more recently the use of acetate as a hemodialysis solution has been limited by its association with cardiovascular instability in patients receiving large volume renal replacement therapy[45,46]. Adverse effects of acetate are frequently observed with both high doses and high rates of acetate infusions, particularly in the setting of hemodialysis. Small quantities of acetate in dialysate solutions have been reported to cause supra-physiological acetate plasma concentrations (50 to 100 μmol/L)[47-49]. In addition, use of acetate solutions as a cardiopulmonary prime has also been reported to cause similar plasma concentrations in patients undergoing cardiac surgery[50], although it is unknown if such concentrations are associated with detrimental or adverse clinical outcomes.

Kirkendol *et al*[51] first reported that sodium acetate produced a dose-related decrease in cardiac contractility and blood pressure in a dog model. These initial reports conflicted with further laboratory research as the same investigators showed that a slow infusion of acetate failed to cause adverse hemodynamic effects[52]. Hypoxia and hypotension are reported adverse effects in patients with chronic kidney disease dialyzed with solutions containing acetate[45,53,54]. In a crossover study involving twelve patients undergoing hemo-diafiltration randomized to either acetate or bicarbonate (acetate free) dialysate, Selby *et al*[55] demonstrated that exposure to acetate free dialysate was associated with less deterioration in systemic hemodynamics, and less suppression of myocardial contractility. Similarly, Jacob *et al*[56] examined the effect of acetate on myocardial energy metabolism and reported that acetate levels of 5 mmol/L impacted negatively on fatty acid metabolism in cardiac tissue and impaired cardiac contractility. Whilst the authors cautioned that their observations might be applicable to other parenterally administered acetate solutions, there have been no human studies to support these findings[56]. In contrast, Nitenberg *et al*[57] evaluated the effect of acetate on cardiac function before and after a sodium acetate infusion during dialysis. Cardiac function improved with plasma acetate concentrations of 3.13 mmol/L. PL 148 was shown to have adverse effects in a model of animal model of hypovolemic shock. In a study comparing four resuscitation crystalloids, animals who received PL 148 had worse survival rates and higher plasma lactate concentrations compared with NS and lactated solutions[58]. Ringer's lactate was considered the most favourable crystalloid due to its lower chloride concentration when compared to NS, and absence of acetate and magnesium when compared to PL 148.

The use of PL 148 with acetate as its organic anion may confer several advantages over the lactate-containing crystalloids. One clinical advantage is that unlike lactate metabolism, acetate metabolism is not entirely dependent on hepatic function. Acetate metabolism is preserved in severe shock, in contrast to lactate metabolism, which can be significantly impaired[59]. Lactate may be an important prognostic indicator after liver resection[60], shock states and critical illness[61,62], with strong associations shown with hyperlactatemia and risk of complications and death. Acetate is metabolised more rapidly than lactate, generating bicarbonate within 15 min after its adminstration[63,64]. Acetate is also more alkalinizing than lactate, which may confer benefit in treating patients who are acidemic who require fluid intervention or resuscitation. Ekblad *et al*[65] showed that a continuous infusion of sodium acetate (3 mmol/kg per 24 h) corrected metabolic acidosis in premature infants. More recently, in a larger clinical trial of 78 critically ill trauma patients resuscitation with sodium acetate as an alternative to NS or Hartmann's solution in patients receiving acetate had stable hemodynamic profiles without evidence of hemodynamic instability at any point[66]. In the patients who received acetate, there was a rapid correction of both metabolic acidosis and hyperchloremia. Other reported advantages of acetate are that its metabolism does not depend on age[67], acetate protects against malnutrition without disturbing glucose homeostasis[68], and unlike lactated solutions, acetate does not affect glucose or insulin concentration[68,69]. The conversion of exogenously administered lactate to glucose *via* gluconeogenesis has been reported to cause significant hyperglycemia[70]. In diabetic patients, intraoperative glucose levels have been shown to double following administration of exogenous lactate solutions[71].

Gluconate: PL 148 contains 23 mmol/L of gluconate.

However, there is limited information about the physiological impact or clinical consequences of gluconate. Approximately 80% of gluconate is eliminated *via* renal mechanisms. Compared with HCO_3, lactate or acetate, gluconate exerts little, if any alkalinizing effect[51,72]; therefore its clinical effects *in vivo* as a metabolically degradable anion appear to be very limited. Gluconate may protect against post ischemic cardiac dysfunction and oxidative injury[73], however there is lack of data on acetate and gluconate levels after PL 148 administration in most surgical settings. In a phase II clinical trial of PL 148 *vs* a bicarbonate-based cardiopulmonary bypass prime solution, there was a significant increase in unmeasured anions levels after PL 148 administration, which was still present, albeit in smaller concentrations prior to cessation of CPB[74]. Liskaser *et al*[19] reported similar findings. The unmeasured anions were attributed to acetate and gluconate. Davies *et al*[50] observed that when PL 148 was administered as a cardiopulmonary bypass pump-prime fluid, there were supra-physiologic plasma levels of acetate and gluconate when compared to a bicarbonate pump prime solution. There were no significant differences in systemic inflammation (as measured by Interleukin-6 levels), and the authors advocated larger scale studies to more precisely assess this phenomenon. The implications of supra-physiological gluconate and acetate levels remain undetermined.

Specific indications for PL 148 for perioperative fluid intervention

General surgical setting: There is a paucity of large-scale prospective trials comparing PL 148 to other fluid buffered (*e.g.*, Hartmann's solution) and non-buffered (*e.g.*, NS) solutions. A summary of the clinical trials pertinent to PL 148 are summarized in Table 2. Whilst an accumulating body of retrospective studies suggest that chloride rich solutions such as NS may directly contribute to iatrogenic hyperchloremic metabolic acidosis and adverse renal outcomes[23,25,75], results from larger prospective studies are still eagerly awaited before conclusive evidence is available to influence practice regarding the use of balanced solutions over NS[36]. Based on the current literature, balanced solutions appear to be more physiological than NS, however at present there is insufficient evidence from clinical trials to unequivocally prove that balanced or buffered crystalloid solutions are associated with improved patient outcomes. Further, at present, there is also insufficient evidence to advocate for the routine use of PL 148 over other commercially available buffered or non-buffered crystalloid. Understanding the physicochemical properties of PL 148 is paramount, as this will allow clinicians to individualise its use taking into consideration patients' comorbidity, pathology, existing fluid deficit, and concurrent biochemical derangements.

Diabetic ketoacidosis: PL 148 may have a beneficial role in patients who present in diabetic ketoacidosis[76,77]. In a randomized controlled clinical trial, diabetic patients admitted to the emergency department with ketoacidosis were resuscitated with either PL 148 or NS. Use of PL 148 prevented the development of a hyperchloremic metabolic acidosis[76]. This study did not comment on glycemic control or overall outcomes of the patients. In a similar study by Chua *et al*[77], the outcomes of patients with diabetic ketoacidosis admitted to three major critical care centres across Australia who received PL 148 or NS were evaluated. Use of PL 148 was associated with a more rapid improvement in metabolic acidosis than those who received NS. Patients receiving PL 148 had less hyperchloremia, improved mean arterial pressure, and higher cumulative urine output. Despite a more rapid improvement in metabolic acidosis, no difference was found in overall glycemic control or length of stay in ICU based on the choice of fluid administered.

Brittle diabetic patients: Unlike lactate metabolism, the metabolism of acetate does adversely affect insulin or glucose homeostasis[68,69]. PL 148 may therefore confer clinically advantages in brittle diabetic patients. In contrast, when lactate was supplied exogenously in solutions, gluconeogenesis was the principal metabolic pathway for lactate metabolism[78,79]. Plasma lactate levels as low as three mmol/L significantly increased the rate of gluconeogenesis from exogenously supplied lactate[80]. Although healthy volunteers showed no increase in glucose concentrations following lactate infusion[78,80,81], patients undergoing major surgery receiving lactated solutions can have significant intra-operative increases in blood glucose levels[70]. In diabetic patients, intraoperative glycemic control may also be significantly impaired following the administration of lactate containing solutions[71].

Liver resection and liver transplantation: The use of lactate free solutions in patients undergoing major liver surgery may be beneficial for several reasons. First, the metabolism of acetate into bicarbonate is not entirely dependent on liver metabolism, in contrast to lactate metabolism, which is more reliant on adequate liver metabolism[59]. Lactated solutions may therefore be inadequately metabolized during the anhepatic phase of liver transplantation, during major liver resection surgery or in patients with acute or chronic liver insufficiency undergoing major surgery. Plasma lactate levels are also an important prognostic marker after liver resection[60], shock states and critical illness[61,62,82]. Two recent studies evaluating fluid intervention in patients undergoing major liver resection supported the notion that lactate in Hartmann's solution can independently increase lactatemia[83,84]. A randomised controlled trial involving 104 donors undergoing right hepatectomy compared acid base status, lactate concentrations and liver function test of patients who received PL 148, or Hartmann's solution[83]. PL 148 resulted in lower lactate and bilirubin levels, lower prothrombin times, and higher albumin levels compared to patients receiving Hart-

Table 2 Summary of the Plasma-Lyte 148 clinical trials

Ref.	Title	Objectives	Patient numbers	Findings
Liskaser *et al*[19]	Role of pump prime in the etiology and pathogenesis of CPB-associated acidosis	RCT that compared the development of metabolic acidosis in patients on CPB who had either Hemaccel- Ringer's Solution, or PL 148 as the pump prime fluid	n = 22	All patients developed a metabolic acidosis when the pump prime fluid was delivered Participants who received Hemaccel-ringer's solution developed a hyperchloremic metabolic acidosis, however participants who received PL 148 developed acidosis as a result of an increase in unmeasured ions, likely acetate and gluconate The acidosis was reversed more quickly with PL 148 compared to NS
Yunos *et al*[24]	The biochemical effects of restricting chloride-rich fluids in intensive care	This study evaluated the acid base effects of administration of chloride-restricted fluids to critically ill patients, compared with unrestricted fluid management	n = 1644	Restriction of chloride rich fluids was associated with a reduction in metabolic acidosis (P < 0.001), standard base excess (P < 0.001) and severe acidemia (P < 0.001) The intervention was associated with a greater incidence of severe metabolic alkalosis (P < 0.001)
Shaw *et al*[25]	Major complications, mortality, and resource utilization after open abdominal surgery: NS compared to PL	This observational study compared the post-operative complications, in-hospital mortality and resource utilization after abdominal surgery between patients who received either NS or PL 148 fluid therapy on the day of surgery	n = 31920	Patients who received PL 148 had lower rates of in-hospital mortality (P < 0.001) and major complications (including renal failure requiring dialysis (P < 0.001), post-operative infection (P < 0.006), blood transfusions (P < 0.001), electrolyte disturbance (P < 0.046) and acidosis investigation (P < 0.001) and intervention (P = 0.02)
Aksu *et al*[31]	Balanced *vs* unbalanced crystalloid resuscitation in a near-fatal model of hemorrhagic shock and the effects on renal oxygenation, oxidative stress, and inflammation	Animal study in which rats were induced into hemorrhagic shock, and were then resuscitated with either no fluid, PL 148 or NS	n = 6	Both PL 148 and NS restored blood pressure during resuscitation NS was associated with hyperchloremia (P < 0.001) and metabolic acidosis (P < 0.05) PL 148 restored acid base balance more effectively than NS PL 148 was associated with improvement in renal oxygen consumption occurred compared to NS (P < 0.05) Systemic inflammation and oxidative stress were similar with NS or PL 148
Chowdhury*et al*[32]	A randomized, controlled, double blind crossover study on the effects of 2L infusions of NS and PL on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers	The authors used MRI to compare the renal blood flow of healthy male volunteers following a 2L infusion of either PL 148 or NS	n = 12	NS was associated with hyperchloremia (P < 0.0001) and metabolic acidosis (P < 0.025) NS was associated with a decrease in a reduction in mean renal artery flow velocity (P = 0.045) and renal cortical tissue perfusion (P = 0.008), findings not observed after PL 148
Young *et al*[35]	Effect of a buffered crystalloid solution *vs* saline on acute kidney injury among patients in the Intensive Care Unit: The SPLIT randomized clinical trial	A double blind, cluster randomized, double-crossover trial conducted in 4 intensive care units. The primary aim was to determine the effects of PL compared with NS on renal complications	n = 2278	No differences in the incidence of acute kidney injury (P = 0.77) No differences in mortality (P = 0.40)
Omron *et al*[42]	A physicochemical model of crystalloid infusion on acid-base status	In this study, authors used a simulated human model in a standard physiological state to compare the effect of 5 different fluids with varying SID values on the acid-base status of the human model when infused up to 10 L	n = 1	Solutions with a SID greater than 24.5 mEq/L resulted in a progressive metabolic alkalosis Solutions with a SID less than 24.5 mEq/L resulted in a progressive metabolic alkalosis PL 148 (SID of 50 mEqu/L) caused a progressive metabolic alkalosis when administered in high volumes

Davies *et al*[50]	Plasma acetate, gluconate and interleukin-6 profiles during and after CPB: A comparison of PL 148 with a bicarbonate-balanced solution	In this study, acetate levels were compared in elective cardiac surgical patients who received either PL 148 or a bicarbonate- balanced crystalloid as the priming fluid for their cardiopulmonary bypass	n = 30	PL 148 was associated with supraphysiological plasma concentrations of acetate (P < 0.0005) and gluconate (P < 0.0005) after institution of CPB Gluconate levels remained persistently elevated at the end of CPB Plasma concentrations of acetate did not completely return to normal levels until 4 h post separation from CPB There were no significant differences in concentrations of IL-6 between the two priming fluids
Traverso *et al*[58]	Fluid resuscitation after an otherwise fatal hemorrhage: I. Crystalloid solutions	An animal model in of hemorrhagic shock comparing four crystalloid solutions (NS, Ringer's lactate, Plasmalyte-A, and Plasmalyte-R) to prevent death after a fatal hemorrhage	n = 116	Ringers lactate provided the best survival when compared to saline and PL After analyses of arterial blood gas values, biochemistry variables, and hemodynamic metrics such as heart rate and aortic pressure, Ringers lactate was considered the most superior crystalloid solution (P value: not stated)
Morgan *et al*[74]	Acid-base effects of a bicarbonate-balanced priming fluid during cardiopulmonary bypass: comparison with PL. A randomised single-blinded study	In this RCT, the authors compared the acid- base effects of a bicarbonate-balanced trial crystalloid with those of PL when administered as a 2-L prime in patients undergoing elective cardiac surgery	n = 20	PL 148 was associated with a metabolic acidosis (P = 0.0001) and an increased strong ion gap secondary to a surge of unmeasured anions (likely acetate and gluconate)
Yunos *et al*[75]	Association between a chloride-liberal *vs* chloride-restrictive IV fluid administration strategy and kidney injury in critically ill adults	This study assessed the rates of kidney injury in patients admitted to ICU who received only chloride- restricted fluids such as PL 148 or Hartmann's solution compared to those that also received fluids that were high in chloride concentration, including NS	n = 1533	The incidence of acute kidney injury decreased significantly in patients who received a chloride-restrictive fluid plan compared to those who received fluids high in chloride concentration (P < 0.001) No differences in hospital mortality, hospital or ICU length of stay were observed
Mahler *et al*[76]	Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis	In this prospective single centre study, patients admitted to the emergency department in diabetic ketoacidosis were resuscitated over at least 4 h with either NS or PL 148, and their serum chloride and bicarbonate levels were monitored and compared	n = 45	Resuscitation with NS was associated with higher serum chloride concentrations (P < 0.001) and lower bicarbonate concentrations (P = 0.020) Resuscitation with PL 148 prevented hyperchloremic metabolic acidosis
Chua *et al*[77]	PL 148 *vs* NS for fluid resuscitation in diabetic ketoacidosis	In this retrospective study, the authors compared the plasma biochemistry, hemodynamic and glycemic control in patients admitted to the ICU for management of ketoacidosis who were resuscitated primarily with PL 148 or NS over the first 12 h	n = 23	PL 148 was associated with less hyperchloremia and a more rapid improvement in metabolic acidosis than those who received NS (P < 0.05) PL 148 improved hemodynamic measures including an improved mean arterial pressure at 2-4 h, and higher cumulative urine output at 4-6 h compared the NS group (P < 0.05) No differences were observed in glycemic control or length of stay in ICU based
Shin *et al*[83]	Lactate and liver function tests after living donor right hepatectomy; a comparison of solutions with and without lactate	A randomised controlled compared the acid- base status, lactate levels and liver function tests in patients undergoing hepatectomy for liver transplant who received PL 148 or Hartmann's solution	n = 104	Immediately post hepatectomy, donors who received PL 148 had significantly lower lactate levels (P = 0.005), lower bilirubin concentrations (P < 0.001), shorter prothrombin time (P = 0.009), and higher albumin levels compared to the Hartmann's group There were no significant differences between the groups in albumin, bilirubin, or prothrombin times on post-operative day 5 There were no significant differences in complications or duration of hospital stay

Weinberg *et al*[84]	The effects of PL 148 *vs* Hartmann's solution during major liver resection: a multicentre, double blind, randomized controlled trial	Multicentre RCT investigating the biochemical effects of Hartmann's solution or PL 148 in patients undergoing major liver resection. Primary outcome: Base Excess immediately after surgery. Secondary outcomes: changes in blood biochemistry and hematology	n = 60	Base excess similar in both groups at completion of surgery (P = 0.17) Postoperatively patients receiving Hartmann's solution were more hyperchloremic (P = 0.01) and hyperlactatemic (P = 0.02) Patients receiving PL 148 had higher plasma magnesium levels (P < 0.001) and lower ionized calcium levels (P < 0.001) No significant differences in pH, bicarbonate, albumin and phosphate levels PT and aPTT were significantly lower in the PL 148 group (P < 0.001, P = 0.007)
MacFarlane *et al*[85]	A comparison of PL 148 and NS for intra-operative fluid replacement	RCT that compared the pre-op and post-operative acid base status of patients who received either NS or PL 148 whilst undergoing major hepatobiliary or pancreatic surgery	n = 30	Intra-operatively, NS was associated with increased plasma concentrations of chloride (P < 0.01), decreased levels of bicarbonate (P < 0.01), and an increased base deficit (P < 0.01), compared to PL 148 Less blood loss and higher postoperative hemoglobin in the PL 148 group) (P = 0.03) Total complications were more frequent in the Hartmann's group (P = 0.007) Hyperchloremic metabolic acidosis occurred in patients receiving NS but not in those receiving PL 148
Hadimioglu *et al*[87]	The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation	A blinded RCT investigating the effects of NS, lactated Ringer's, or PL 148 on changes in acid-base balance, potassium and lactate levels during kidney transplantation. Urine volume, serum creatinine, and creatinine clearance were recorded on postoperative days 1, 2, 3 and 7	n = 60	Patients receiving NS had lower pH levels, and higher chloride levels (P value not stated) Lactate levels increased significantly in patients who received Ringer's lactate (P value not stated) No significant changes in acid-base measures or lactate levels occurred in patients who received PL 148 Potassium levels were not significantly changed in any group The best metabolic profile was maintained in patients who receive PL 148
Kim *et al*[88]	Comparison of the effects of NS versus PL on acid-base balance during living donor kidney transplantation using the Stewart and base excess methods	RCT compared the effects of NS and PL 148 on acid-base balance and electrolytes during living donor kidney transplantation using the Stewart and base excess methods	n = 60	Significantly lower values of pH, base excess, and effective strong ion differences during the post-reperfusion period in the NS group (P < 0.05) Hyperchloremic metabolic acidosis present in the NS group (P < 0.05) No differences between the groups in early postoperative graft function (P = 0.3)
Potura *et al*[89]	An acetate-buffered balanced crystalloid *vs* NS in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial	RCT that evaluated the impact of NS *vs* a chloride-reduced, acetate-buffered crystalloid on the incidence of hyperkalemia during cadaveric renal transplantation. The incidence of metabolic acidosis and kidney function were secondary aims	n = 150	The incidence of hyperkalemia differed by less than 17% between groups (P = 0.56) Use of balanced crystalloid resulted in less hyperchloremia (P < 0.001) and metabolic acidosis (P < 0.001) Significantly more patients in the NS group required administration of catecholamines for circulatory support (P = 0.03)
Smith *et al*[99]	Cost-minimization analysis of two fluid products for resuscitation of critically injured trauma patients	A retrospective cost-minimization analysis evaluating fluid and drug acquisition costs, materials and nurse labor costs, and costs associated with electrolyte replacement in patients who received PL 148 or NS	n = 46	Substitution of PL 148 for NS for fluid resuscitation during the first 24 hours after trauma was associated with decreased magnesium replacement requirements (P < 0.001) and a net cost benefit to the institution

Smith *et al*[100]	Does saline resuscitation affect mechanisms of coagulopathy in critically ill trauma patients? An exploratory analysis	An exploratory analysis of a subset of subjects enrolled in a randomized trial comparing the effect of resuscitation with PL 148 and NS on acidosis and electrolyte abnormalities	n = 18	Patients receiving NS were more acidemic at 6 h (mean pH saline 7.31 *vs* PL 148; base excess NS -5.3 mmol/L *vs* 0.6 mmol) (P value: not stated) Kinetics time was shorter (P = 0.06) and alpha angle was significantly greater (P = 0.008) in the PL 148 group NS did not alter endogenous thrombin potential: (P > 0.1) for all variables
Song *et al*[101]	The effect of 0.9% saline *vs* PL 148 on coagulation in patients undergoing lumbar spinal surgery; a randomized controlled trial	This study compared the effect of PL 148 to NS on coagulation assessed by rotation thrombo-elastometry (ROTEM) and acid-base balance in the aforementioned patients	n = 50	Patients receiving NS developed a transient hyperchloremic acidosis (P < 0.05) Coagulation assessed by ROTEM analysis and the amount of blood loss was similar between the groups: (P > 0.1 for all variables)
Young *et al*[102]	Saline *vs* PL in initial resuscitation of trauma patients: a randomized trial	RCT that evaluated the acid-base status of patients who were resuscitated with either PL or NS for the first 24-h post major trauma	n = 46	Significantly greater improvement in base excess (estimated difference 4.1 mmol/L) and less hyperchloremia (estimated difference 7 mmol/L) in patients who were resuscitated with PL compared to those resuscitated with NS (P value: not stated)
Story *et al*[103]	Cognitive changes after saline or PL 148 infusion in healthy volunteers: a multiple blinded, randomized, crossover trial	Randomized, crossover, blinded study of healthy adult volunteers. On separate days, participants received 30 mL/kg over 1 h of either NS or PL. Primary endpoint: reaction time index after infusion - a validated metric of cognitive function	n = 25	NS was also associated with greater metabolic acidosis (P < 0.001) NS was also associated with higher serum chloride levels (P < 0.001) No difference in measures of cognition after infusions of PL 148 or NS (P = 0.39)
Noritomi *et al*[104]	Impact of PL 148 pH 7.4 on acid-base status and hemodynamics in a model of controlled hemorrhagic shock	After controlled hemorrhagic shock was induced, animals were resuscitated with NS, Ringer's lactate solution or PL 148	n = 18	Resuscitation with all three fluids restored cardiac output, and urinary output Resuscitation with PL 148 and Hartmann's Solution both resulted in a reduction in chloride concentration, and increased base excess Resuscitation with NS was associated with an increased chloride concentration (P = 0.018), reduction of base excess (P = 0.042) and a metabolic acidosis (P = 0.045)

PL 148: Plasma-Lyte 148; NS: Normal saline 0.9%; RCT: Randomized clinical trial; CPB: Cardiopulmonary bypass; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; SID: Strong ion difference; ICU: Intensive care unit; IL: Interleukin.

mann's solution. In this single centre study no significant differences in complications or duration of hospital stay between groups were reported. Recently, however, in a multicentre trial evaluating patients undergoing major liver resection[84], patients who received PL 148 had improved biochemical and hematological profiles (acid base homeostasis, electrolyte balance and coagulation status) as well as fewer complications and reduced length of stay. Finally a smaller study by McFarlane *et al*[85] compared the pre-op and post-op acid base status of patients who received either NS or PL 148 whilst undergoing major hepatobiliary or pancreatic surgery. Consistent with the other studies above, patients who received NS intra-operatively were more hyperchloremic and acidemic compared to those who received PL 148. The most favourable crystalloid solution for patients undergoing major liver surgery is still unknown[86].

Renal transplantation: Traditionally, NS is advocated peri-operatively for renal transplant recipients due to concerns about hyperkalemia from balanced solutions, which contain potassium. Although NS is widely advocated in this setting, recent evidence suggests balanced crystalloids such as PL 148 or Hartmann's may be more appropriate. Hadimioglu *et al*[87] performed a randomised clinical trial comparing PL 148, Hartmann's solution, and NS as intraoperative fluid replacement in 90 patients undergoing renal transplant. Those receiving NS had higher chloride, lower pH and lower base excess than the other two groups. Those patients receiving Hartmann's had elevated lactate levels. Potassium levels, urine output, serum urea and creatinine and creatinine clearance were similar between the groups. The authors concluded that all three fluids appear safe in short-duration uncomplicated renal transplant surgery, but the metabolic profile was best maintained with PL 148. Four other randomised controlled trials reported acid-base metrics as primary outcomes[88-91]. All were

underpowered to adequately report endpoints such as hyperkalemia, requirements for dialysis, delayed and long-term graft function, and survival. Two of these studies used an acetate based crystalloid solution for fluid intervention[89,91]. Kim *et al*[88] studied the effects of NS and PL 148 on acid-base homeostasis in patients undergoing living donor kidney transplantation. There was significant hyperchloremic metabolic acidosis in the NS group, but no difference in early postoperative graft function. More recently, Potura *et al*[89] evaluated the effects of NS *vs* a chloride-reduced, acetate-buffered solution (similar in composition to PL 148) on the incidence of hyperkalemia in 150 patients undergoing cadaveric renal transplantation. The incidence of hyperkalemia was not statistically different between the groups. However, use of the buffered solution resulted in less hyperchloremia and metabolic acidosis, and a lower requirement for vasoactive medications.

Raised intracranial pressure and hypo-osmolar states: Administration of hypo-osmolar solutions such as Hartmann's solution may worsen cerebral oedema and increase intracranial pressure in neurosurgical patients with critical brain injury or existing raised intracranial pressure. Larger volumes of Ringers lactate are well known to reduce plasma osmolality[92] and result in transient increases in intracranial pressure[93]. The magnitude of the increase in intracranial pressure can be predicted from the reduction of plasma osmolality[9]. In animal models, for every mOsmol/kg reduction in plasma osmolality, there is a mean increase in intracranial pressure of 1.5 mmHg[92,94-98]. Iso-osmolar solutions such as PL 148 or NS may not impact on plasma osmolality to the same extent as hypo-osmolar solutions and may be advantageous in this setting. PL 148 may be advantageous compared to Hartmann's solution in the setting of fluid overload states and iso-osmolar hyponatremia, such as that which occurs in transurethral resection of the prostate syndrome. Given NS's greater tonicity compared to PL 148, NS may be the preferred crystalloid in this setting.

Costs of Plasma-Lyte 148

Currently the net acquisition cost of PL 148 varies significantly between different countries and even between different states within the same country. In Australia, list prices and actual hospital acquisition price differ in accordance with state, individual hospital, local tenders and preferred supplier agreements. In New Zealand, there is different pricing again due to the Pharmaceutical Management Agency, which actively manages government spending on medicines in order to maximize value for medicines, achieving the best health outcomes for the amount of public money spent. In Australia and New Zealand net acquisition costs of 1000 mL PL 148 varies between $2.00 and $5.00; in other countries such as China and South Korea prices appear to be similar. In contrast, net acquisition costs for a 1000 mL bag of Hartmann's solution or NS is Australia is currently less than $2.00. Recently, a retrospective cost-minimization analysis evaluated drug acquisition and expenses related with electrolyte replacement in critically injured trauma patients treated with NS or PL 148[99]. The use of PL 148 was associated with a higher fluid acquisition costs and a decreased need for magnesium supplementation[100]. Considering consumable supplies and nursing labor costs, there was a $12.35 daily cost-differential in patients who received PL 148. Substitution of PL 148 for NS was correlated with reduced magnesium supplementation therapy and overall net cost-benefits for the hospital.

In conclusion, administration of IV fluids is fundamental to the optimal management of patients in anesthesia and critical care medicine. The selection of the appropriate fluid for administration is often based on clinician preference, and to date there is a lack of large-scale prospective research comparing the safety, efficacy and indications of the different types of crystalloid solutions. Whilst NS is the most common IV fluid crystalloid worldwide, large-scale observational studies and small-randomized trials suggest a strong association between its use and adverse biochemical and clinical outcomes. Emerging data supports the use of buffered crystalloid solutions in preference to NS in improving physicochemical outcomes; however currently there is insufficient evidence to recommend this change in practice. Further large randomized controlled trials assessing the comparative effectiveness of PL 148 and NS in higher risk patients by measuring clinically important outcomes such as mortality are currently underway[36].

Use of PL 148 should be based on a detailed knowledge of its physicochemical properties, and the pathophysiological condition of the patient. The ideal approach for perioperative fluid therapy should therefore always be individualized: Qualitatively: Fluid with suitable physicochemical composition individualized to patients' physiological state and specific type of surgery, and quantitatively: The right amount of fluid at the right time and at the right rate.

COMMENTS

Background

The use of intravenous fluids for maintenance therapy and resuscitation in anesthesia and critical care medicine is universal. There is marked variation in perioperative fluid selection, frequently determined by institution and clinician preference. Such practice variation is related to the paucity of prospective evidence evaluating the comparative safety and efficacy of available crystalloid solutions for both fluid resuscitation and maintenance therapy in the perioperative setting. The authors present a comprehensive review of Plasma-Lyte 148 (PL 148), comparing its physiochemical properties to other commonly available crystalloids solutions.

Research frontiers

PL 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition that closely reflects human plasma. Emerging data supports the use of buffered crystalloid solutions in preference to sodium

chloride (0.9%) in improving physicochemical and clinical outcomes.

Innovations and breakthroughs

There is a paucity of large-scale prospective trials comparing Plasma-Lyte 148 (PL 148) to other fluid buffered (*e.g.*, Hartmann's solution) and non-buffered (*e.g.*, sodium chloride, 0.9%) solutions. Based on the current literature, balanced or buffered solutions appear to be more physiological than sodium chloride (0.9%), however at present there is insufficient evidence from prospective clinical trials to unequivocally prove that such solutions are associated with improved patient outcomes. Further, at present, there is insufficient evidence to advocate for the routine use of PL 148 over other commercially available buffered or non-buffered crystalloid.

Applications

Unlike lactate, acetate metabolism is not entirely dependent on preserved liver function for its metabolism, and the metabolism of acetate does adversely affect insulin or glucose homeostasis. Therefore, PL 148 may more beneficial than a lactate buffered solution in critically ill patients with liver hypoperfusion, liver insufficiency, or for patients undergoing complex liver surgery. PL 148 may also be a favourable solution in brittle diabetic patients. PL 148 is a more alkalinising solution than sodium chloride and Hartmann's solution, and may have a role in correcting severe metabolic academic states where fluid intervention is indicated. Administration of hypo-osmolar solutions such as Hartmann's solution may worsen cerebral oedema and increase intracranial pressure in neurosurgical patients with critical brain injury or existing raised intracranial pressure. Similar to sodium chloride (0.9%), Plasma-Lyte is isotonic, and may be a suitable solution for fluid therapy in this setting. Use of PL 148 should be based on a detailed knowledge of its physicochemical properties, and the pathophysiological condition of the patient. The ideal approach for perioperative fluid therapy should be individualized: qualitatively: Fluid with suitable physicochemical composition individualized to patients' physiological state and specific type of surgery, and quantitatively: The right amount of fluid at the right time and at the right rate.

Terminology

A crystalloid solution is any solution containing electrolytes and non electrolytes. A balanced or buffered crystalloid solution is a crystalloid solution with a physiochemical composition that closely reflects human plasma.

Peer-review

The authors reviewed clinical studies of PL 148. The manuscript is valuable and well written.

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