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Controversies in fluid therapy

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SUMMARY

Intravenous fluid therapy has become a ubiquitous intervention in both human and veterinary medicine. The field of fluid therapy is characterised by numerous controversies, and despite their widespread use, fluids should be considered as drugs, as their use is associated with potential side effects and complications. This paper will review the differences between crystalloids and colloids, and how their clinical use has changed according to recent scientific evidence. Due to their theoretical advantages, hydroxyethyl starches (HES) have become the most commonly used colloids in both human and veterinary medicine. However, the results of human studies have revealed clear adverse effects on renal and haemostatic functions and an increase in mortality when comparing colloids versus crystalloids for fluid resuscitation. A quantitative toxicity has also been identified and excessive fluid resuscitation appears to be associated with an adverse outcome. These recent studies should prompt the veterinary profession to undertake an appraisal of current fluid therapy practices and recommendations that have thus far been largely based on theoretical benefits rather than clinical evidence. In this review we will focus on some common controversies and how our approach to fluid therapy may be adapted in light of the most recent veterinary and human data.

Key Words: synthetic colloids, hydroxyethyl starches, complications, coagulopathy, kidney injury

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Introduction

The first report in the medical literature of the intravenous administration of a salt-based solution was described in 1832 by Thomas Latta for the treatment of patients affected by cholera[1]. Since then, intravenous fluid therapy has become a ubiquitous intervention in both human and veterinary medicine and it represents a cornerstone in the treatment of ill patients. The field of fluid therapy is characterised by numerous controversies regarding whether there are optimal fluid types, optimal doses and even whether there is a preferable timing and rate of fluid administration. Despite widespread use, fluid therapy is associated with potential side effects and complications, as recently revealed by the results of several large human randomised clinical trials [2,3,4]. These recent studies in the human field should prompt the veterinary profession to undertake an appraisal of current fluid therapy practices and recommendations that have been thus far largely based on theoretical benefits rather than clinical evidence. In this review we will focus on some common controversies and how our approach to fluid therapy may be adapted in light of the most recent veterinary and human data.

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Basic principles of fluid therapy

To be able to appreciate the nuances of fluid therapy a basic understanding of normal body fluid physiology is required. Total body water (TBW) accounts for approximately 60% of total body weight. Total body water is distributed between the intracellular fluid compartment (approximately 66%) and the extracellular fluid compartment (approximately 33%). These two spaces are separated by cell membranes. The extracellular fluid compartment is, in turn, further subdivided into an intravascular (8% TBW) and an interstitial space (25% TBW) [5], and these compartments are separated by the capillary wall (Figure 1).

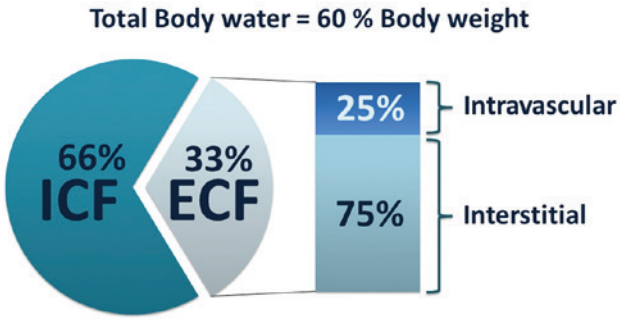

Figure 1. Distribution of total body water (TBW) within the body showing the proportion allocated into the intracellular and extracellular fluid compartments.

The barriers between fluid compartments have different permeability to different solutes based on size, charge and conformation. This selective permeability, along with hydrostatic and oncotic forces (i.e. Starling forces), determines the movement of fluids and electrolytes between compartments. Two other concepts that also play a role in the movement of fluid between compartments are osmolarity and oncotic pressure. Osmolarity is a measure of the number of particles present in a solution, independently of their size or weight. Water tends to distribute between compartments due to osmolarity gradients (osmotic pressure). Oncotic pressure, also known as colloid osmotic pressure, is a particular type of osmotic pressure that is generated by colloid molecules present in solutions.

Clinical signs associated with fluid deficits vary accordingly to the compartment affected (Table 1). Dehydration is defined as total body water deficit, while hypovolemia indicates a purely intravascular volume deficit. The total intravascular volume, including both plasma and cellular components, is estimated to be approximately 88 ml/kg in dogs and 66 ml/kg in cats [6]. The intravascular volume, despite containing only a small proportion of the TBW, is the main determinant of cardiac preload and, as such, plays a fundamental role in maintaining cardiovascular stability. Preload, along with cardiac contractility and afterload, determines cardiac output and blood flow to peripheral tissues (perfusion). As a consequence of this, during hypovolemia, oxygen delivery to peripheral tissues is affected: when the metabolic needs of the body are no longer matched by the blood flow provided by the cardiovascular system, circulatory shock ensues. If left untreated circulatory shock will result in organ dysfunction and eventually death. Therefore, rapidly restoring and maintaining an effective intravascular volume is essential to reverse the progression of the shock state. This therapeutic intervention is referred to as fluid resuscitation and will be the main focus on this review. Other common reasons to administer fluids include restoration of the interstitial and intracellular fluid balance (i.e. rehydration), compensation for on-going fluid losses and to induce diuresis and maintain acid-base and electrolyte homeostasis.

Types of fluids

Fluids used in veterinary patients can be classified into

Table 1. Differentiation of hypoperfusion from dehydration via clinical signs

Signs consistent with hypoperfusion	Signs consistent with dehydration
Increased heart rate	Dry mucous membranes
Hyperdynamic or hypodynamic pulses	Prolonged skin tenting
Hypothermia or cold distal limbs	Normal pulses
Prolonged capillary refill time	Sunken eyeballs
Pale mucous membranes	

4 basic types: crystalloids, colloids, haemoglobin-based oxygen carriers and blood products [7]. Crystalloids are solutions of water and electrolytes or glucose. Some formulations might also contain buffers (e.g. lactate, acetate or gluconate) that, once administered, are metabolised to bicarbonate and can influence acid-base balance. Crystalloids are classified into hypotonic, isotonic or hypertonic solutions based on their relative osmolarity compared to plasma. Isotonic fluids have an osmolarity that is similar to that of plasma (approximately 300 mOsm/L), while hypertonic and hypotonic fluids have an osmolarity that is, respectively, higher and lower than plasma. Isotonic solutions are the most commonly used type of crystalloids. Hypotonic solutions are contraindicated during fluid resuscitation and their use should be reserved to treat specific conditions (e.g. treatment of severe electrolyte imbalances). Hypertonic solutions, and in particular hypertonic saline, may be useful in certain cases that require fluid resuscitation; a dramatic increase in plasma osmolarity leads to a shift of water from the interstitium and intracellular fluid compartments to the intravascular space, resulting in a transient intravascular volume expansion. Isotonic crystalloids available in clinical practice include normal saline (0.9% NaCl) and balanced solutions (e.g. compound sodium lactate, Hartmann's, Ringer's lactate solution, Ringer's acetate solution, Plasma-Lyte). Balanced solutions differ from normal saline in the fact that they contain electrolytes in more physiological concentrations, closely resembling the electrolyte composition of human plasma.

Shortly after administration of crystalloids most of the infused volume will redistribute to the interstitium and intracellular space and by 1 hour only 20-25% of the infused volume will still be within the intravascular space [6]. With this in mind, one can see that if intravascular volume expansion is the main therapeutic target, crystalloid fluid therapy would seem to be an inefficient way of achieving this and their use might promote the formation of interstitial oedema (Figure 2).

Colloids are high-molecular-weight compounds (molecular weight higher than 30 KDa) that, in the normal physiological condition, do not readily leave the intravascular space and contribute to maintaining, or possibly improving, the patient's plasma oncotic pressure. Colloids are classified as synthetic (e.g. hydroxyethyl starches, gelatins, dextrans) or natural (e.g. plasma, albumin solutions, blood). The potential benefits of colloids include prolonged intravascular

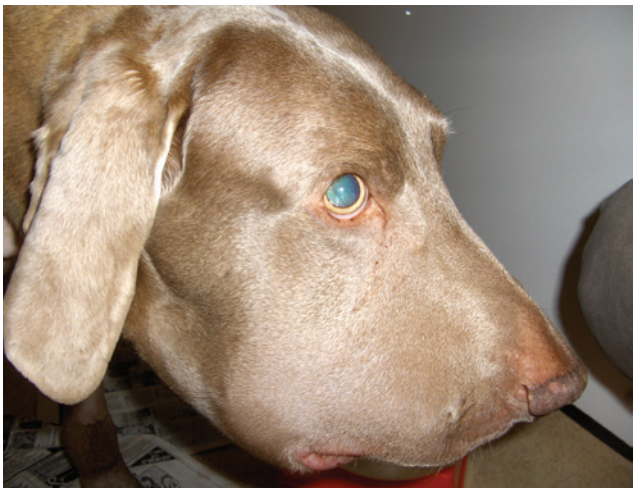

Figure 2. Dog with marked interstitial oedema where fluid has accumulated in the extracellular fluid compartment.

effect, smaller volume requirements and decreased risk of oedema formation when compared with crystalloids [8]. Therefore, if the goal of fluid administration is to address hypovolemia, colloids seem to present some obvious advantages over crystalloids. Ideal colloid solutions should be isotonic, iso-oncotic, rapidly degradable, inexpensive and have minimal side effects [9]. On first inspection, hydroxyethyl-starch solutions (HES) are the colloids that most closely match these criteria. For this reason they have become, up to recently, the most commonly used colloids in both human and veterinary medicine.

HES are synthesised from amylopectin, a highly branched polymer of glucose, and chemically modified by substitution of some hydroxyl- with hydroxyethyl-residues. These modifications provide some of the desired characteristics of colloidal fluid solutions. The various preparations of HES are classified based on their molecular weight, molar substitution (number of hydroxyethyl- residues per unit of glucose), pattern of substitution (C2:C6 ratio) and type of solutions in which they are suspended (e.g., balanced or unbalanced crystalloid solutions). Higher molecular weights and molar substitutions are associated with a longer half-life. Despite their widespread use and their perceived better safety profile compared to other synthetic colloids, HES use is associated with numerous side effects.

Undesirable side effects

Coagulopathy

Coagulopathy is one of the most common side effects associated with the use of synthetic colloids. The mechanism of this coagulopathy is not fully understood,

but some of the proposed pathways include decreased circulating factor VIII and von Willebrand factor concentration, impairment of platelet function and interference with fibrin polymerization [10]. These effects have been reported in dogs as well, although the clinical significance of the abnormalities reported is undetermined [11-15]. It should be noted that current veterinary dose recommendations for colloids (approximately 50 ml/kg/day for low molecular weight HES and 20 ml/kg/day for high molecular weight HES) are not based on efficacy data, but on human safety limits developed to minimise the risk of bleeding [8]. The coagulation disorder associated with HES administration appears to be proportional to the dose administered and the molecular weight and molar substitution of the molecule used. To reduce these risks, novel colloid solutions were developed with a lower molecular weight and lower degree of hydroxyethyl molar substitution [9].

Renal dysfunction

Renal dysfunction is another commonly discussed complication induced by colloid administration in people and this complication has become the focal point of the controversy surrounding the use of starch-based colloids in critically ill patients. All synthetic colloids undergo renal excretion and therefore have the potential to cause acute kidney injury (AKI). The first reports on colloid-induced renal failure were published in the late 1960s in association with the use of dextrans [16,17], but in more recent years, the potential for inducing kidney damage has been reported in other colloids classes [18]. Several hypotheses have been formulated to explain AKI following colloid administration [9]. The increase in the intra-glomerular COP determines a decrease in glomerular filtration rate. The filtration of colloid molecules in the glomerulus increases intra-tubular viscosity and decreases urine flow. In addition, some molecules are re-absorbed by the proximal tubular epithelial cells where they induce vacuolar lesions. This can result in cellular swelling, with an additional decrease in urine flow. Renal interstitial inflammation has also been reported [19].

Colloids vs. crystalloids

HES solution should be theoretically less nephrotoxic given their biochemical characteristics. However, tubular lesions were noticed with the use of high-molar substitution HES in brain dead kidney donors [20]. Studies regarding the renal safety of colloids started to appear in the early 1990s[21]. A trend similar to that observed with coagulopathy appeared: the use of solutions with higher concentrations, higher molecular weight and molar substitution colloids were associated with increased risk of renal toxicity. Low molecular weight, molar substitution and iso-oncotic HES appeared to have the best safety profile [22].

Despite their theoretical advantages HES were approved for medical use without adequate testing regarding safety and efficacy [21]. Up to very recently, limited evidence had been in support of colloids over crystalloids for fluid resuscitation. A Cochrane Collaboration meta-analysis published in 2007 concluded that "…as colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, their use should be limited to randomised clinical trials" [23].

In 2008 the first large randomised clinical trial (RCT) comparing HES versus crystalloids for fluid resuscitation was published [2]. This study revealed a dose related effect linking HES administration with higher incidence of AKI, need for renal replacement therapy (a form of haemodialysis) and number of blood transfusions. In 2011 numerous studies from a leading author regarding the safety and efficacy of starch-based colloids were retracted by a number of journals due to scientific misconduct and data fabrication [24], decreasing even further the level of evidence in support of HES use. The following year two other large high-quality RCT (6S and CHEST studies) investigating the use of HES versus crystalloids for fluid resuscitation in critically ill patients were published [3,4]. These studies confirmed the increased need for renal replacement therapy and blood transfusions associated with the use of HES and also showed a significant increase in mortality in the most severe population treated with HES. Based on these data the most recent Surviving Sepsis Guidelines [25] advised against the use of HES for the treatment of severe sepsis and septic shock. An updated Cochrane Collaboration meta-analysis published in 2013 failed to identify any benefit of the administration of colloids (any) versus crystalloids, and concluded that "… it is difficult to see how HES use can be justified in clinical practice."[26] Another meta-analysis focused on the effect of HES on kidney function and identified an increased risk of developing AKI and a higher need for renal replacement therapy [27]. These two meta-analyses revealed that the risk associated with HES administration is independent from the type of HES or the severity of the population treated. As a consequence, the European Medicines

Agency recommended the suspension of the marketing authorisation for all products containing HES [28] and the Food and Drug Administration of the United States issued a warning against the use of HES in critically ill patients [29]. At the time of writing HES-containing solutions have been withdrawn from the market in several European countries, although the European Union has ratified a recommendation allowing the use of HES in some selected situations such as hypovolaemia not associated with sepsis or burns [30]. Veterinary access to HES depends on local medical regulatory agencies authorising the trade of these products.

To date, there are no reports of nephrotoxicity induced by the use of HES in veterinary patients, but both renal lesions and renal dysfunction have been reported in experimental studies in dogs receiving dextran [17,31] and the pathophysiology of the nephrotoxicity appears to be similar across different classes of colloids. Although there is currently no evidence that HES-based colloids can worsen outcome in veterinary patients these fluids should be used cautiously, especially in patients predisposed to coagulopathy, AKI or with severe sepsis. Studies evaluating the incidence of AKI in veterinary patients treated with starch-based colloids are urgently needed.

It should be noted that the cost of colloids is significantly higher compared to crystalloids just as they are in human medicine, and this aspect should not be overlooked when deciding what type of solution to use for fluid resuscitation. In the context that resuscitation with colloids offers no real benefits in outcome, justification for their use can be problematic.

Other colloid solutions are available as alternatives to HES: gelatins, dextrans, haemoglobin-based oxygen carriers (HBOC), albumin and plasma. Gelatins are derived from bovine collagen and have a low molecular weight (30-35 KDa). Their immediate volume effect is similar to that of HES, but due to their low molecular weight they determine a much shorter duration of volume expansion. Compared to HES, the use of gelatins is associated with a higher risk of anaphylactic reactions [9]. There have also been concerns that the use of gelatins may pose a risk of inducing renal dysfunction, although this is not well described [9]. Dextrans are polysaccharides synthesised from sucrose by bacterial fermentation. Dextrans have the worst safety profile among colloids in terms of coagulopathy, renal dysfunction and for these reasons are not used commonly in human medicine. Oxyglobin® is a veterinary-specific stroma-free HBOC derived from bovine haemoglobin and licensed for the treatment of anaemia in the dog. Compared to other colloids, HBOC has the advantage of providing additional oxygen carrying capacity that can thereby improve tissue oxygenation. The use of HBOC has been demonstrated to enable more rapid achievement of resuscitation endpoints when compared with HES in both experimental and clinical veterinary studies [32,33,34]. However, it should be noted that HBOC has not been approved for human use due to safety concerns, and its use in veterinary patients is associated with significant side effects, especially in terms of volume overload [35]. Albumin has recently substituted HES as the most used colloid solution in human medicine, although there is no extensive evidence of a clinical benefit over crystalloids alone [25,36]. The use of human serum albumin in critically-ill veterinary patients can be associated with both immediate and delayed side effects [37,38]. Its use in healthy patients under experimental conditions was associated with sometimes fatal hypersensitivity reactions [39]. A canine-specific serum albumin had been commercially produced in North America, but it is no longer available. Plasma can also be used for fluid resuscitation and has a better safety profile compared to albumin solution, however, the risk of transfusion reactions remains. It is also important to note that plasma is not particularly effective as a plasma expander, nor is it practical as it is usually stored frozen and not cost effective given the need for large volumes in order to alter the COP of the patient.

When compared with crystalloid fluid solutions, colloids are considered more potent plasma expanders and this is partly due to their greater persistence within the intravascular space. This means that smaller volumes of colloids are required to expand the intravascular space compared with crystalloid solutions. The ratio of colloids:crystalloids that needs to be administered to achieve a similar volume effect is approximately 1:4, and this has been confirmed in several experimental studies [40,41]. An interesting finding that has emerged from several human RCT is that the actual volume effect of HES in clinical settings is less than previously thought. The ratio of HES to crystalloids administered to achieve similar resuscitation endpoints actually only ranged from 1:1 to 1:1.6, far below the predicted 1:4 ratio [2,3,4]. This raises questions on the validity of the assumption that colloids are more effective plasma expanders. This discrepancy in the volume effect could be explained through the concept of “context

sensitivity." This concept proposes that the volume effect of administered fluid is variable and depends on the cardiovascular context of the patient. The cardiovascular context takes into account derangements in vascular permeability, intravascular volume and hydration status. In other words, the highly desirable behaviour of colloids may only be apparent in subjects with normal vascular endothelium and these advantages may not be appreciated in critically ill patients [42,43].

Lending support to the aforementioned concept, a major advancement in the understanding of fluid homeostasis has been made possible by the recent characterisation of the endothelial glycocalyx layer (EGL) (Figure 3) [44]. This is an active interface between the blood and the capillary wall and appears to be the main determinant of vascular permeability. This structure can be damaged in several conditions, such as hypoalbuminaemia, sepsis, hypoxia, hyperglycaemia or hypervolemia. When the EGL is intact vascular permeability is preserved and colloids have a volume effect that exceeds that of crystalloids. However, damage to this structure leads to an increase in vascular permeability and consequently a loss of the "volume advantage" offered by the colloids.

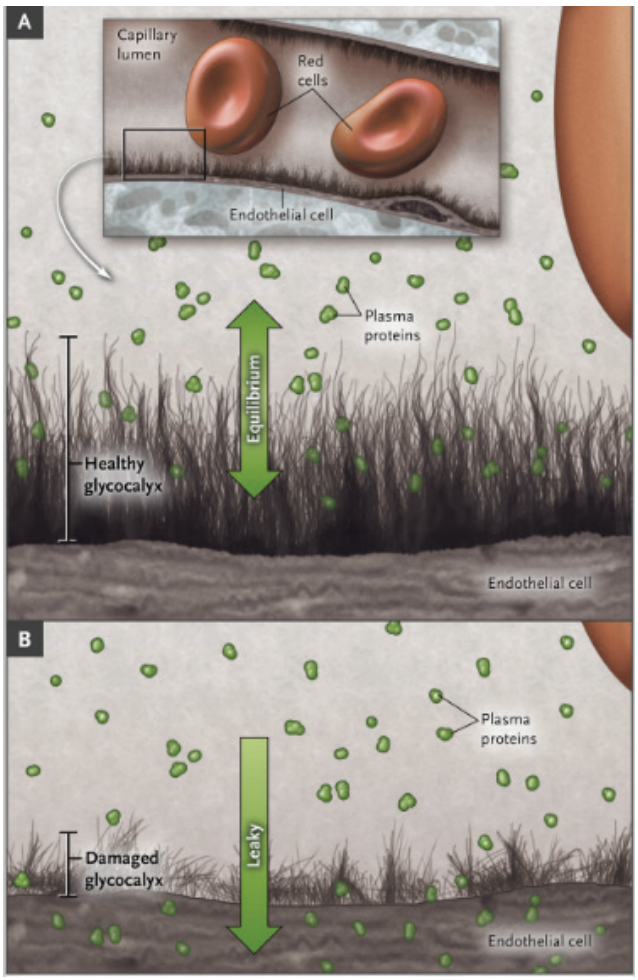

Figure 3: Endothelial glycocalyx layer in health (A) and damaged by disease (B). The integrity of the endothelial glycocalyx layer may dictate the permeability of membranes and may explain why there are differences in the response to colloid fluid therapy depending on the state of the animal. From N Engl J Med, Myburgh GA, Mythen MG. Resuscitation fluids. 369:1244. Copyright © (2013) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Are crystalloids safe?

Given the side effects associated with the use of colloids, crystalloids are expected to continue to play a major role in human fluid resuscitation despite the higher risk of interstitial oedema. Sodium chloride (0.9% Saline) has historically been the most used solution for volume expansion in human patients. However, due to its composition, the use of 0.9% saline is associated with the development of hyperchloraemic metabolic acidosis [45]. When compared to balanced crystalloids solutions (e.g. lactated Ringer, Plasma-Lyte, Compounded Sodium Lactate), 0.9% saline use is associated with a higher morbidity and mortality [46,47,48]. The role of chloride-load and hyperchloraemic metabolic acidosis in veterinary critical illness is unknown, but it seems prudent to prefer the use of balanced crystalloids over saline for fluid resuscitation.

An alternative to isotonic crystalloids for fluid resuscitation is hypertonic saline. These solutions contain a higher percentage of sodium chloride of 7.2% and 23.4%. As such they have a very high osmolarity and once infused produce an elevation in intravascular sodium. This in turn creates a concentration gradient that drives fluids from the interstitial and intracellular to the intravascular space with a short lived (20-30 minutes) intravascular volume expansion. The theoretical advantage is achieving fluid resuscitation whilst infusing a smaller volume of fluid. The displacement of fluid from the interstitium might also play a role in the treatment of traumatic brain injury. The use of hypertonic saline requires adequate intracellular and interstitial hydration and can cause bradycardia and hypernatremia as possible complications [5]. The safety and efficacy of hypertonic saline has not been established in human medicine and results of preliminary studies are contradictory [43].

Along this qualitative toxicity a quantitative toxicity has also been described. A positive fluid balance is associated

with the development of interstitial oedema and worse outcome [49]. In a trial comparing restrictive versus liberal fluid strategies, the latter has been associated with a reduced morbidity [50]. As we will see in the next paragraphs clinical research is focusing on methods to identify the adequate dose of fluid to administer.

How much fluid to give?

A variety of strategies have been developed to optimise tissue perfusion in critically ill patients and have been collectively defined as goal-directed therapies. The application of goal-directed therapy protocols has shown to improve both morbidity and mortality in people [51]. Restoring and maintaining an adequate circulating blood volume is considered the most important aspect in goal-directed therapy, however identifying the adequate fluid dose for each individual patient is not an easy task. Insufficient fluid resuscitation will be associated with inadequate tissue perfusion, but excessive fluid administration will also have negative consequences through the development of interstitial oedema, leading to organ dysfunction [52]. Therefore, identifying those patients that will benefit from fluid administration is essential. This concept is referred to as fluid responsiveness, and is defined as the ability of a patient's cardiac output to improve following the administration of intravenous fluid therapy. Historically fluid-responsiveness was assessed through "static" indexes of cardiac preload (e.g. central venous pressure), but such markers appear to be inadequate [53]. For this reason, a new approach using "dynamic" indexes has been developed and is based on evaluating the effect of changes in cardiac preload on the cardiac output [54]. An example of a dynamic index of fluid responsiveness evaluated in veterinary patients is pulse pressure variability (PPV) [54]. Arterial pulse pressure is used as a surrogate marker of stroke volume and its variation is assessed in patients undergoing mechanical ventilation. Due to lung-heart interactions, each respiratory cycle decreases preload in a predictable manner and this causes a decrease in cardiac output proportional to the patient "fluid-dependency." Therefore, patients that will benefit from fluid administration will have a proportionally higher PPV. This index has been validated in dogs [55,56]. The use of PPV in veterinary practice is limited by the need to place an arterial catheter, a procedure that can be technically challenging, especially in small or collapsed patients, and carries a risk of bleeding and infection. Moreover, only some monitors support algorithms that allow the measurement of PPV. The application of an early goal-directed haemodynamic optimisation protocol has been recently described in dogs undergoing surgery for pyometra [57]. Further studies are needed to identify the ideal end-points of resuscitation and if a goal-directed protocol would improve the outcome in veterinary patients.

Conclusions

Current evidence in human medicine suggest that the use of colloids over crystalloids carries very little benefit, with the potential of significant side effects associated with the use of synthetic colloids. Experimental veterinary studies show theoretical advantages of colloids, but these effects have not proven to be associated with an improvement in outcome. Moreover, although the nephrotoxic effects of HES have not yet been observed in veterinary patients, the mechanisms of toxicity seem to be similar across all synthetic colloid classes, independent of their composition, concentration and molecular size. Further studies will be needed to assess the safety profile of synthetic colloids in veterinary patients. In the meantime, we believe that a precautionary principle should be applied to colloid administration in veterinary patients, and their use should be limited to selected circumstances. Synthetic colloids should be used with particular caution in critically ill patients with sepsis or an established acute kidney injury. In conclusion, all fluids should be considered as drugs, and as such have the potential to cause toxicity if administered incorrectly. Context sensitivity appears essential in the selection process of fluid type, dose, and timing of administration. Fluid resuscitation protocols will therefore have to be tailored based on the clinical status of each individual patient. Veterinary research should focus on the identification of criteria for patients' stratification in order to develop individualised fluid resuscitation plans.

The authors declare no conflict of interests.

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