Norges miljø- og biovitenskapelige universitet

Bacheloroppgave 2021
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Risk Factors Associated with Crystalloid Fluid Therapy in Dogs and Cats

Risikofaktorer for å utvikle bivirkninger ved krystalloid væskebehandling hos hund og katt

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Bachelor Dyrepleie

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Summary

Title: Risk factors of crystalloid fluid therapy in dogs and cats.

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Background and aim: There is a continuous exchange of fluids and electrolytes between the body compartments and disturbances in the fluid balance can be fatal. Crystalloids are fluids that easily cross the intravascular barrier and are most often used for intravenous fluid therapy in veterinary medicine. Fluid therapy stabilizes and corrects fluid, electrolyte and acid-base balance, but can also be associated with negative side effects and there are various risk factors that can affect the results of fluid therapy. In this systematic literature study, we aimed to obtain more knowledge about these risk factors of crystalloid fluid therapy in cats and dogs.

Materials and methods: We searched three different databases for peer-reviewed articles written in English from the years 2000-2020. The keywords used were dogs, cats, fluid therapy, iv fluids, intravenous, risks and risk factors. The search resulted in three articles to analyze.

Results: From the articles analyzed we found that being critically ill, getting high doses of fluids and undergoing surgery were identified as risk factors for developing side effects of fluid therapy in both dogs and cats. Meanwhile, the development of a heart murmur or gallop heart sounds and being hyponatremic were risk factors only identified in cats.

Conclusion: There are few articles that have studied the risk factors of fluid therapy in dogs and cats and most of the current fluid therapy recommendations in veterinary medicine are based on human medicine research. We believe that more research on dogs and cats would be beneficial to improve fluid therapy in the veterinary field.

Definitions

Acidemia	An increase in the hydrogen ion concentration of the blood, resulting in decreased pH.
Antidiuretic hormones (ADH)	A hormone that reduces urine output by promoting the reabsorption of water by the kidneys.
APPLE score	Acute Patient Physiologic and Laboratory Evaluation Score
Cardiac output	The volume of blood being pumped by the heart, by each of the heart ventricles, per unit time.
Colloids solution	Emulsion; heterogeneous mixtures that contain much larger sized solutes than those found in solutions
Colloid osmotic pressure	The difference between the osmotic pressure of blood and the osmotic pressure of interstitial fluid or lymph
Crystalloids solution	A crystalloid fluid is an aqueous solution of mineral salts and other small, water-soluble molecules.
Dehydration	Loss of total body water from all spaces
Edema	An abnormal accumulation of fluid, either localized or generalized, within the tissues or cavities of the body.
Extracellular fluid (ECF)	The body fluid located outside the cells
Fluid therapy	Supplying the body with fluids to substitute for fluid loss
Fluid overload (FO)/ Hypervolemia	Medical condition where there is too much intravascular fluid in the body.
Fluid overload percent (%FO)	Percentage of fluid overload adjusted for body weight and fluid input versus output.
Homeostasis	The maintenance of balance in the body
Hydrostatic pressure	The force that propels a liquid

Hypernatremia	Increased levels of sodium in the blood
Hyperkalemia	An excess level of potassium in the blood
Hypertonic	A solution with a higher osmotic pressure compared to another fluid
Hypoglycemia	Blood sugar (glucose) level is lower than normal
Hypokalemia	Decreased levels of potassium in the blood
Hyponatremia	Decreased levels of sodium in the blood
Hypothermia	Decreased body temperature
Hypotonic	A solution with a lower osmotic pressure compared to another fluid
Hypovolemia	Abnormally low intravascular volume
Iatrogenic	hospital-acquired
Interstitial compartment/space	The interstitial compartment is the fluid-filled space that surrounds the cells in a tissue
Intracellular fluid (ICF)	The body fluid that is contained within the cells
Intravascular compartment/space	The fluid compartment located inside the blood vessels
Intravascular volume	Amount of fluid found in the intravascular space
Isotonic	A solution with the same osmotic pressure as another fluid

Maintenance fluid solution	Solutions used to replace daily sodium losses and fluid.
Osmolarity	Osmolarity refers to the number of solute particles per 1 L of solvent
Osmotic pressure (OMP)	A term that is associated with properties of thin membranes so that they let through water and small molecules, but not large molecules, colloids.
RAAS	Hormone system within the body. The Renin - Angiotensin - Aldosterone System
Replacement fluid solution	Solutions used for rapid replacement of intravascular fluid volume
Risk factors	Factors that may exacerbate, cause or increase the chances of negative side effects

Introduction

Fluid therapy relates to the practice of supplying the body with fluids to substitute for normal or abnormal fluid losses. Human physicians already in the early 17th century believed that significant blood loss should be replenished with extraneous fluids. In 1638 physician William Harvey discovered blood vessels and the circulatory system from here on there were different experiments with intravenous administrations and blood transfusion. These early experiments often had fatal consequences as there was little knowledge and serious complications (Millam, 1996). Until the 1830s and the cholera epidemic, most attempts of intravenous administration were of blood transfusion. It is during this time that the first attempts of fluid resuscitation with saline fluids are made and the effects of dehydration on the blood are mentioned in human medicine (Foëx, 2003; Kampmeier et al., 2014; Srinivasa & Hill, 2012). William Latta was the first to document successful results with intravenous fluid administration and developed different solutions for administration during the epidemic. But it was not until the late 19th century that loss of fluids was acknowledged as a cause of death in some patients and that intravenous fluid therapy became a frequent part of treatment (Foëx, 2003; Srinivasa & Hill, 2012). The first production of physiological saline (0,9% NaCl) as an isotonic crystalloid replacement solution happened in 1875 and the Ringer's solution in 1880 which was later modified into lactated Ringers solution (LRS) in the 1930s (Driessen & Brainard, 2006). In the years that followed, during the 20th century, war and the need to save patients from hemorrhagic shock, fluid loss and higher use of anaesthetics during operations lead to faster discoveries within fluid therapy and the invention of new equipment and different types of fluids for administration (Kampmeier et al., 2014; Millam, 1996).

The development of veterinary medicine has been connected to human medicine and a lot of knowledge regarding fluid therapy was simply adopted into veterinary medicine. Although the first intravenous infusion that we know of in animals dates all the way back to 1658, when Sir Christopher Wren made a mixture of wine, ale, opium and liver of antimony to be infused in a dog (Millam, 1996), early veterinary medicine was heavily centred around equine veterinary medicine and life stock animals. It's not until the later part of the 19th century and the 20th century that small animal medicine became a relevant field within veterinary medicine (Jones, 2017). Studies on fluid therapy and small animals can be found dating back

to the 60s but in general fluid therapy in small animal veterinary medicine is a subject still under advancement.

Physiology

To administer fluid therapy properly, one has to know where fluids reside within the body and how they are lost during the normal and abnormal physiologic state. The healthy animal contains about 60 to 70% of water, which is found inside and surrounding the cells. Fluids found inside the cells are called intracellular fluids (ICF) and the fluid that is found outside the cells is called extracellular fluids (ECF). The ICF is found inside the bilayered cell plasma membrane and is in osmotic equilibrium with ECF. Water and small dissolved solutes move among the fluid spaces in the body based on their concentration gradients and the osmotic effects of larger less diffusible macromolecules. The capillary walls are permeable to electrolytes and enable water and small dissolved solutes to move readily between the intravascular and interstitial fluid spaces. The movement of these fluids and electrolytes is governed by hydrostatic and oncotic pressure (Byers, 2017; Mensack, 2008). Hydrostatic pressure is the pressure exerted by any fluid in a confined space and is generated by the pressure of fluid on the capillary walls. The oncotic pressure is the osmotic pressure generated by large molecules in solution. There is a continual exchange between the fluid compartments in the body, which provides nourishment to cells and removes waste products. Hydrostatic pressure and oncotic pressure work against each other to produce the exchange between the fluid compartments. The plasma osmolality and oncotic pressures in an organism that can determine the direction of fluid movement within the system; therefore, the relative concentration of ions and protein in the solvent. Plasma osmolality and osmoregulation maintain the body's electrolyte–water balance (Byers, 2017).

In a healthy animal, water is lost via urine, feces, respiration and cutaneous evaporation. When animals get dehydrated an increase in plasma osmolarity occurs (Ackerman, 2016 s.478-479). Cells then begin to lose water and shrivel because they are now hypo-osmolar compared to the surroundings. Osmolality is the millimoles of solute per kilogram of solution. Increased osmolality is detected by osmoreceptors in the hypothalamus. This releases antidiuretic hormone (ADH) from the posterior pituitary gland and stimulates thirst. ADH plays essential roles in the control of the body's osmotic balance, blood pressure regulation, sodium homeostasis, and kidney function. It primarily affects the ability of the kidney to

reabsorb water; when present, ADH induces expression of water transport proteins in the late distal tubule nephron and collecting duct to increase water reabsorption. Water flows from a compartment of low osmolality inside the tubules to a compartment with high osmolality, the interstitial fluid in the renal medulla. Severe dehydration often leads to low blood pressure and which in turn triggers renin secretion from the kidney, renin converts angiotensin I to II. That increases aldosterone release from the adrenals. This is all part of the renin-angiotensin-aldosterone system (Ackerman, 2016 s.478; Taylor & Jones,2021). The renin-angiotensin-aldosterone system (RAAS) is a critical regulator of blood volume, systemic vascular resistance and fluid balance. It is composed of three major compounds: renin, angiotensin II and aldosterone. These compounds act to elevate arterial pressure in response to decreased renal blood pressure by increasing reabsorption of natrium from the nephrons (aldosterone) and increasing total peripheral resistance in the circulatory system (angiotensin II). Angiotensin II can also cause the release of the ADH, which mentioned above can stimulate thirst among other things (Cuzzo B, 2020).

Extracellular fluids

The ECF can be divided into three compartments, the intravascular compartment, the interstitial compartment and transcellular fluid which contains only about 1% of the bodyweight (Ackerman, 2016 s. 478). The interstitial compartment surrounds cells and facilitates the movement of ions, proteins and nutrients across cell membranes. Approximately 25% of the ECF is located in the intravascular compartment. In the interstitial space, fluids are continuously turned over and recollected by the lymphatic vessels and approximately 75% of the ECF is located in the interstitial compartment (Byers, 2017).

Electrolytes and acid-base balance

Body fluids are filled with many different kinds of particles called solutes. The solutes can either have or not have an electrical charge. Charged particles are called ions and they can either be positively charged or negatively charged. Negatively charged ions are called anions and positively charged ions are called cations. Because anions and cations are capable of conducting an electrical current in solutions, they are called electrolytes. Acid and bases dissociate in water and can conduct an electrical impulse and are therefore also considered electrolytes. Acids release hydrogen ions and bases release hydroxyl ions when in solution.

Body fluids are rich in hydrogen and hydroxyl ions and their relative proportion determines the acidity or alkalinity of the fluid. Electrolytes, acid/base balance and fluid are intrinsically linked and it is difficult to consider one without the other (Colville et al., 2016 s. 28).

Dissolved in the body fluids are chemical materials that are essential for the body's metabolism and which play a part in controlling the movement of fluid around the body. Many medical conditions and surgical procedures cause an upset in the fluid balance and if nothing is done to correct this the animal may become severely dehydrated or go into shock and die. The electrolyte balance in the body has a strong connection to the fluid balance in the body. Fluid imbalances can cause electrolyte imbalance and vice versa. Fluid therapy can thus also have an influence on the body's electrolyte balance (Ackerman, 2016 s. 355). Two of the most important electrolytes are sodium and potassium. They are essential for normal bodily function. Disruption in the sodium balance affects osmolality in the body and fluid distribution. Sodium and potassium are also important to maintain the cell membrane potential, a vital part of muscle contraction and nerve impulse transmission. Disruption of potassium levels can affect the cardiac muscle, the skeletal system and the kidneys. The kidneys play an important role in maintaining the balance of potassium intake (Ackerman, 2016 s. 356-357).

Administration routes

Fluid therapy can be considered as drug therapy with dose ranges for different conditions and potential side effects and therefore treatment plans need to be re-evaluated and reformulated according to changes in the status of the patient. Before commencing fluid therapy a number of factors should be taken into consideration, such as type of fluid, fluid volume needed infusion rate, route of administration and location where the fluid is needed in the body (Davis et al., 2013). The simplest route of fluid therapy is by oral consumption. One can also administer fluids subcutaneously, that is when fluid is injected under the skin. Other more invasive routes of fluid therapy are intraperitoneal, intraosseous and intravenous (Ackerman, 2016). Intraperitoneal administration, injecting fluids into the body cavity is not often used as there are risks of infections or of damaging abdominal organs on top of that absorption of fluids intraperitoneally is slower and can also be more uncomfortable for patients (Lee & Cohn, 2017). Intraosseous administration is injecting fluid directly into the bone marrow. The last route, and the route this study is about, is intravenous fluid therapy which is when we

administer fluids directly into the veins. This route is essential for critically ill patients and patients that need long term fluid therapy (Tello & Perez-Freytes, 2017).

When is fluid therapy needed?

Fluid loss

Intravenous fluids are used to treat or prevent dehydration, treat hypovolemic shock and intravascular volume depletion, correct acid-base and electrolyte abnormalities and fluid loss (Mazzaferro, 2008). Fluid loss can be split into four categories: pure water loss, hypotonic fluid loss, isotonic fluid loss and hypertonic fluid loss. Pure water loss makes the ECF tonicity rise that causes rapid translocation of water from the larger intracellular compartment to establish a new elevated level of body tonicity. Pure water loss can therefore lead to hypertonicity and contraction of all body water compartments proportional to their share of total body water (Bhave & Neilson, 2011). Pure water loss is however not common in small animals. Hypertonic fluid loss is when the loss of electrolytes is greater than the loss of water. Isotonic fluid loss takes place when sodium and water are lost together. There is no change in the osmolarity, so no water movement occurs until the compensatory mechanisms have begun. Both hypertonic and isotonic fluid loss is caused by diarrhea, vomiting, renal and kidney failure (Ackerman, 2016 s. 481; Taylor & Jones, 2021). Hypotonic fluid loss happens when the loss of water exceeds the loss of sodium. This happens due to severe secretory diarrhea (Ackerman, 2016 s.481).

Dehydration

Fluid loss leads to dehydration, loss of water from all the body compartments. This can occur through vomiting and diarrhea, polyuria, increased evaporation due to pyrexia/hyperthermia or panting, wound exudation, third space losses into the pleural, peritoneal cavity or interstitial space (Ackerman, 2016 s.480). Dehydration can be categorized into different percent of dehydration. Dehydration under 5% usually does not cause any clinical signs other than dry mucous membranes and lethargy. If the dehydration is between 6 - 12% severity of reduced skin turgor, increased heart rate and reduced pulse can occur. At 12 - 15% the fluid loss will be sufficient to start displaying signs of hypovolemic shock. If the dehydration reaches 15% the patient will be moribund and severely hypovolemic (Davis et al., 2013;

Ackerman, 2016 s.480). An estimate of dehydration is done by physical examination, measuring heart frequency, pulse and blood samples. Checking the skin turgor by pulling on the animal's skin and letting go is one of the most common ways of checking their hydration status. The best place to do so is via a skin tent over the dorsum of the neck or on the lateral thorax. Checking the colour, moisture and capillary filling time of the mucous membrane is also used to assess dehydration. When checking the hydration status you should be aware that older animals have less elasticity in their skin, obese animals have often more elasticity in their skin (Byers, 2017).

Normovolemic patients

Fluid therapy can also be used in patients where the main problem is not fluid loss and dehydration. Such as patients suffering from shock trauma, hypothermia, sepsis, malnutrition and help with low blood pressure (Driessen & Brainard, 2006; Macintire, 2008). It's common practice that patients undergoing anaesthesia, even for a short period, should get fluid therapy to help maintain homeostasis both pre, peri and post-operative as anaesthesia can cause changes in the fluid balance of the body (Fantoni & Shih, 2017). Inhalation anaesthesia has a tendency to cause vasodilatation affecting blood pressure and hemorrhages during operations also affect the blood volume. Fluid therapy during this time helps control vascular tone, maintain circulatory volume and improve cardiac output (Fantoni & Shih, 2017). Patients suffering from endocrine disorders and for example, hypoglycemia, can at times also have the need for fluid therapy to get glucose (Boysen, 2008) and fluid diuresis is helpful in patients with renal disease or to hasten the elimination of toxins that are excreted by the kidneys (Grauer, 1998).

Types of fluids for fluid administration

There are different categories of fluids available for intravenous use in small animal patients. The two main types of fluids are crystalloids or colloids. Crystalloids can be split into three categories, hypertonic, isotonic and hypotonic solutions. Colloids can be split into two main groups, synthetic and natural colloids.

Crystalloids

Crystalloids are fluids that contain small solutes with a molecular weight less than 500 Da (Fantoni & Shih, 2017). Crystalloid solutions consist primarily of water with a sodium or glucose base, plus the addition of other electrolytes or buffers (Mensack, 2008). Which crystalloid fluid is most beneficial for the patient's needs depends on the concentration of electrolytes the different solutes have. As mentioned before the different groups of crystalloids are hypotonic, isotonic and hypertonic solutions, the difference between them lies in their tonicity, their osmotic pressure compared to plasma. On some occasions, dextrose in water is mentioned as its own separate type of fluid, but it can be categorized as a hypertonic solution (Mensack, 2008).

Isotonic solutions

Isotonic solutions have the same osmotic pressure as plasma and have a sodium concentration of about 140 mml/L (Byers, 2017). Isotonic solutions can be split into maintenance or replacement solutions depending on their electrolyte concentration and they also differ in buffer concentration (Rudloff & Kirby, 1998). Isotonic solutions are used for rapid replacement of intravascular volume, electrolytes and to correct dehydration, they are the most commonly used fluids in veterinary medicine (Ackerman, 2016 s.484). When administering isotonic crystalloids only about 20-25% of the infused volume remains in the intravascular compartment 1 hour post-infusion, the rest enters the interstitial compartment (Rudloff & Kirby, 1998). Therefore, large amounts of isotonic solutions must be administered to replace intravascular volume (Annane et al., 2013; Brunkhorst et al., 2008). Isotonic solutions with buffers tend to correct acidemia faster than buffer-free fluids (Rudloff & Kirby, 1998). Because potassium loss increases during aldosterone release and sodium conservation it is important to supplement isotonic solutions with potassium if administered for longer periods of time to be able to compensate for those losses (Byers, 2017). Examples of isotonic solutions are lactated Ringers, Plasma-Lyte, Normosol-R, and 0.9% sodium chloride (Byers, 2017; Mensack, 2008).

Two of the most commonly used isotonic solutions in veterinary medicine are 0.9% Sodium chloride and lactated Ringer's solution, there is much discussion on which of the two fluids is best to use. Isotonic sodium chloride is a non-buffered solution typically used when there is a

decrease in sodium and chloride or when there is a higher potassium concentration (Barea Mendoza et al., 2016; Rudloff & Kirby, 1998). Lactated Ringer's solution is a buffered isotonic solution used when patients need added calcium or potassium and not recommended in patients with hyperkalemia (Rudloff & Kirby, 1998). The buffer, lactate, should not affect lactate levels in patients with a healthy liver (Rudloff & Kirby, 1998). Lactated Ringer has at times been associated with hyponatremia while 0.9% sodium chloride has been used to lower the risks of hyponatremia (Ricciuti et al., 2020; Shamim et al., 2014). Lactated Ringer has other positive aspects such as increasing plasma bicarbonate and preventing hyperchloremic acidosis (Ricciuti et al., 2020). It has been questioned whether the use of sodium chloride, especially in critically ill patients can lead to hyperchloremia, an electrolyte disorder associated with renal artery vasoconstriction, acute kidney injury, hyperchloremic metabolic acidosis and gastrointestinal dysfunction (Friederich et al., 2019; Van Zyl et al., 2011). Research on this has given varied results but a human medicine study review from 2017 found that the risk of side effects and mortality did not increase when using sodium chloride contra other types of fluids and that adverse results had more to do with errors in fluid therapy management, monitoring and lack of knowledge (Zhou et al., 2018).

Hypotonic solutions

Hypotonic solutions have a lower osmotic pressure than plasma with a sodium concentration of about 70 mmol/L which equates to the sodium concentration in the body (Byers, 2017). Less than 10% of the administered volume remains within the intravascular compartment 1 hour after infusion. They are appropriate for long-term administration and infused at just the rates necessary to replace daily sodium losses in patients that are unable to maintain proper fluid and electrolyte intake (Rudloff & Kirby, 1998). Hypotonic solutions may also be supplemented with potassium to better balance the patients´ electrolyte requirements. These fluids include 0.45%NaCl, 0.18%NaCl with 4% or 5% glucose. Some fluids may have 2,5% dextrose added instead of glucose, as the two are functionally the same substance (Byers, 2017; Mensack, 2008).

Hypertonic solutions

Hypertonic solutions, solutions with higher osmotic pressure in comparison to plasma are typically used to increase intravascular volume. The high amount of sodium in hypertonic

solutions creates a steep osmotic gradient forcing the body to move fluid from the interstitial space and into the intravascular space (Rudloff & Kirby, 1998). This causes a rapid intravascular volume expansion, an effect that only lasts about 30 minutes because the body redistributes the sodium by diffusion (Byers, 2017). For this reason, hypertonic solutions can be used on patients suffering from shock due to acute hypovolemia (Rudloff & Kirby, 1998). For a prolonged effect of hypertonic solutions, it is recommended to give them combined with a colloid solution (Mensack, 2008). Isotonic solutions should be administered after hypertonic solutions to make up for the interstitial fluid that moved to the intravascular space (Mensack, 2008). Examples of hypertonic solutions are NaCl with a 7%, 7.5% or 23% concentration and dextrose in water (Byers, 2017). Dextrose in water is commonly supplemented to approximate plasma tonicity and prevent hemolysis (Byers, 2017). However once administered the body will metabolize the dextrose and only the water will remain, with no other active solute there is little effect of these types of fluids, and they are not commonly used in veterinary medicine (Mensack, 2008).

Colloids

Colloid solutions are fluids with larger molecules that, unlike crystalloids, don’t easily cross the intravascular barrier therefore a smaller amount of colloid fluids is needed to increase OMP and intravascular volume then what would be needed from crystalloid solutions. How long colloids remain in the intravascular compartment depends on their molecular size; the bigger the molecules, the longer they stay (Fantoni & Shih, 2017). The different kinds of synthetic colloids are gelatins, dextrans, hydroxyethyl starches and polymerized hemoglobin (Ackerman, 2016 s.486). Natural colloids are substances like fresh frozen plasma, hemoglobin-based oxygen carriers and serum albumin. These types of fluids can be used in specific situations to provide patients with clotting factors, albumin, fibrinogen and hemoglobin (Byers, 2017). Administration of colloids can be split into low volume administration and high volume administration. High volume administration is commonly used during hypovolemic shock or active hemorrhages. Low volume administration is used to support intravascular volume and for volume resuscitation in animals who are vulnerable to increases in the interstitial fluid volume (Rudloff & Kirby, 1998). Colloids in general are less used in veterinary medicine compared to crystalloids, it's because of this that we have chosen to not include colloids in our study.

Side Effects of Fluid Therapy

Although an important part of treatment in veterinary medicine, intravenous fluid therapy can be associated with different negative side effects, unwanted outcomes of fluid therapy. Factors that can influence the negative side effects are the type of fluid being administered, the rate of administration and the patient's condition.

Electrolyte disorders

When fluid therapy causes electrolyte disorders it affects electrolyte concentrations in the entire body, however the way we measure electrolyte disorders is by their concentration in plasma. Hypernatremia is when there are high concentrations of sodium, extracellular sodium of 145 mmol/L or higher is considered hypernatremia. Administration of sodium rich fluids like hypertonic saline in large volumes or at high rates can cause hypervolemic hypernatremia in the extracellular space (Ackerman, 2016 s. 355, s.482; Mazzaferro, 2008). Hypertonic saline can cause sodium levels in plasma to rise faster than what the body can balance, attracting water to the extracellular space by osmosis and causing intracellular dehydration (Ackerman, 2016 s.355) . Hyponatremia on the other hand is when there are sodium concentration levels lower than 130-135 mmol/L. Normovolemic hyponatremia can occur in patients receiving hypotonic fluid therapy (Ackerman, 2016 s.482). Rapid infusion of hypotonic solutions can cause a rise of volume in blood plasma while simultaneously diluting the sodium concentration in plasma resulting in hyponatremia. Similarly, excessive amounts of hypotonic solutions can dilute other plasma electrolytes (Ackerman, 2016 s. 484).

Hypokalemia is a condition in which there are low levels of potassium in the body. Severe hypokalemia can promote refractory ventricular arrhythmias, muscle cramping, muscle weakness, lethargy, anorexia, ileus and cervical ventroflexion (Ackerman, 2016 s.483; Complications of). Hypokalemia is a common side effect of long-term administration of isotonic solutions without supplemented potassium (Ackerman, 2016 s.482; Mazzaferro, 2008). Animals lose potassium through urine, and this process is enhanced during aldosterone release and sodium conservation (Byers, 2017). Though isotonic solutions like lactated Ringer Solution, Plasma-Lyte and Normosol-R have potassium concentrations comparable to that of potassium concentrations in plasma they are not able to make up for the larger amounts of potassium loss during long-term fluid therapy oftentimes resulting in fluid therapy-induced

hypokalemia (Byers, 2017). Administering fluids with supplemented potassium too quickly or in excessive amounts can also lead to hyperkalemia (Fantoni & Shih, 2017). Hyperkalemia is an acute life-threatening condition and it can affect myocardial conduction (Ackerman, 2016 s.482).

Fluid overload

Another serious negative side effect of fluid therapy can be hypervolemia. Large increases in hydrostatic pressure can occur as a result of fluid therapy and this can lead to interstitial and third space fluid accumulation (Mazzaferro, 2008). Edemas caused by fluid therapy is a condition called fluid overload (Cavanagh et al., 2016). Fluid overload can manifest itself as peripheral edemas, pulmonary edemas or leakage of fluid into the peritoneal or pleural cavities (Thomovsky et al., 2016). Fluid overload negatively affects cardiac, renal and pulmonary function, gastrointestinal motility, tissue oxygenation and wound healing, capillary and lymphatic flow (Cavanagh et al., 2016; Mazzaferro, 2008). A way to measure fluid overload is by using fluid overload percent (%FO), a formula created in a study for human medicine that takes into account fluid in, fluid out and bodyweight (Cavanagh et al., 2016). Fluid overload is associated with higher mortality and morbidity rates and negative side effects can develop before visible edemas appear, one should therefore try to diagnose fluid overload as soon as possible (Cavanagh et al., 2016). When monitoring patients receiving fluid therapy one should check their respiratory status and look out for shivering, restlessness, serous nasal discharge, chemosis, tachypnea, cough and pulmonary crackles, all signs that can appear before peripheral edemas (Mazzaferro, 2008).

Cerebral edema

Administration of hypotonic solutions can cause sodium dilution in blood plasma, this can be a reason for a sudden drop in sodium levels. In the response to decreased levels of sodium, extracellular water will shift into cells where there is higher tonicity in an attempt to normalize the gradient and thereby causing cerebral edema or central pontine myelinolysis. Therefore, cerebral edema is often caused by rapid correction, with the use of fluids, of hyponatremia. The brain is unable to recapture the lost osmolytes with the rapid correction of hypernatremia, leading to dehydration of brain tissue and demyelination of white matter.

Patients suffering from chronic hyponatremia have therefore higher risk for developing cerebral edema (Danyalian & Heller, 2021).

Other

The kidneys are the primary route of excretion for all synthetic colloids and thus colloids are associated with side effects involving renal injury (Ackerman, 2016 s.486). Renal injury can happen when the bigger molecules in solutes, commonly from colloid solutions blocking the renal tubules or causing osmotic nephrosis. Osmotic nephrosis is a disease mostly caused by hypertonic fluids or by polysaccharide-based plasma volume expander. This condition changes the tubular epithelial cells in the kidneys and affects the structure and the function of the kidneys (Matsushita et al., 2018). Colloid administration has also been associated with higher risks of coagulopathies and anaphylaxis (Hahn, 2017; Laxenaire et al., 1994).

Purpose and issue

There are different underlying factors in the patient that can heighten the chances of them getting both visible and not visible side effects, sometimes even outright causing them, these underlying factors are the risk factors of fluid therapy. Even though it may be the veterinarian's job to choose a treatment for the patients, veterinary nurses are the ones that monitor and care for hospitalized patients and knowing the risk factors and complications is important since most of the hospitalized patients get fluid therapy (Davis, 2015). So far we have been taught how to administer general fluid therapy but we do not have a lot of knowledge about high-risk patients. The overall purpose of the study was to obtain more knowledge about the risk factors that affect unwanted side effects for patients receiving fluid therapy with crystalloids. The main question or the issue is ¨what are the risk factors of fluid therapy with crystalloids in dogs and cats? ¨.

Materials and methods

Databases and keywords

Our bachelor thesis is a systematic literature study. To find our literature we used the PubMed, Oria and CAB databases. Using the PICO method to determine our search words; fluid therapy, iv fluids, intravenous, risk factors, risks, dogs and cats (Table 1). We conducted a search by splitting the keywords up into different combinations with both dogs and cats as shown in table 2.

Inclusion and exclusion criteria

We set a timeframe of twenty years, 2000-2020, to get the most recent research material with updated practice. We included only one language, English, and only peer reviewed articles were included. Other than this we had no boundaries for which publishing journal the articles should be from nor what type of study design the experiment followed. Risk factors in fluid therapy in dogs or cats had to be addressed in the experiment for the articles to be included. We excluded all review articles, articles that were about human medicine and articles that did not address risk factors in fluid therapy in dogs and cats. An overview of the literature search is presented in Table 3.

Table 1. PICO method to find keywords.

PICO	Keywords
P	dogs, cats
I	intravenous, fluid therapy, iv fluids
C	-
O	risk factors, risks

Table 2. Overview of keyword combinations used in our search

Different keyword combinations	fluid therapy AND risk factors OR risks AND dogs*
	iv fluids AND risk factors OR risks AND dogs*
	intravenous AND risk factors OR risks AND dogs*
	fluid therapy AND risk factors OR risks AND cats*
	iv fluids AND risk factors OR risks AND cats*
	intravenous AND risk factors OR risks AND cats*

Table 3. Overview of databases, keywords and criteria for the literature search

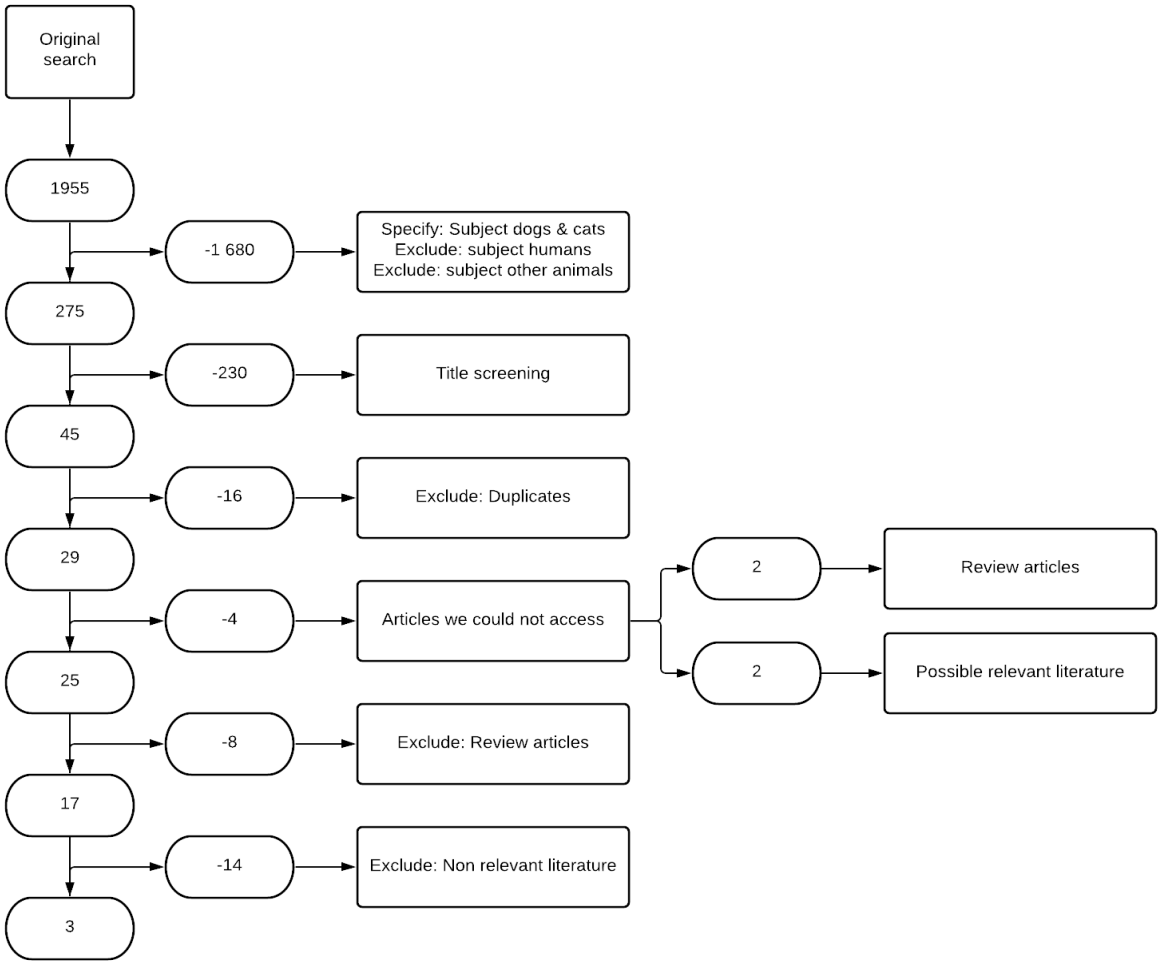
Databases	PubMed, CAB Abstracts, Oria
Language	English
Time frame	2000-2020
Search words	fluid therapy, intravenous, iv fluids, risk factors, risks, dogs*, cats*
Inclusion criteria	experimental articles, veterinary medicine subject: animals, fluid therapy, risk factors, dogs, cats
Exclusion criteria	human medicine, review articles, pharmacology, parasitology, focus on colloids. Journals of: zoology, poultry, dairy, horses animal: swine, horses, rodents, sheep, cattle, bunnies

Elimination process

The search we reference to here was conducted on the 26/02/2021. The elimination process is demonstrated in Figure 1 down below. We got a total of 1 955 articles from the original search that were peer-reviewed, written in English and within the timeframe of 2000-2020. 1 680 of these articles had gotten through our search even though they had humans or other animals besides dogs and cats as subjects, once removed we were left with 275 articles. The titles of these 275 articles were screened for relevance to our study, leaving only 45 articles. 16 out of 45 were duplicates, after excluding them we had 29 articles left. There were 4 articles we could not access as the databases either did not give a link forward or the links

provided were expired with no way for us to find the articles and attempt to buy them with help of the university library. From the abstract provided in the databases, we were able to deduce that at least 2 of these articles were review articles and therefore would not have been a part of our study anyway. The other two remained as possibly relevant literature. Out of the 25 remaining articles on our list, 8 of them were review articles, leaving us with 17 articles. We then excluded non-relevant literature based on the purpose of the articles. Some of the excluded articles researched risk factors not related to fluid therapy itself and its side effects but more so other aspects surrounding fluid therapy, for example, such as intravenous catheters. Some of them compared different fluid therapy strategies on a healthy and equal study population, with a focus on minimizing all possible risk factors. 14 out of 17 were considered non-relevant and we ended up with 3 articles.

Figure 1. The elimination process for the current literature study



Results

The three articles we analyzed are presented chronologically in table 4. The studies from article 1 and article 2 were conducted in university teaching hospitals and the study from article 3 in a referral veterinary hospital.

Article 1

The premise of the first article was to determine if critically ill dogs had an increased risk of fluid overload during hospitalization compared to less ill dogs and if fluid overload was associated with increased mortality during hospitalization by calculating percent fluid overload (%FO). This study was an observational case-control study, and the data was collected in the years 2010 to 2012 comparing critically ill dogs (group C) to healthy and stable postoperative dogs (group S) admitted to the ICU. Group C contained 34 critically ill dogs and group S contained 15 stable postoperative dogs. Group S had undergone orthopaedic surgery, hemilaminectomy or cervical ventral slot surgery. Group C was diagnosed with vehicular polytrauma, acute kidney injury, postoperative abdominal surgery, postoperative urinary tract surgery, sepsis, acute abdomen with gastrointestinal surgery, toxicoses, wounds, a neurologic disease affecting the brain, neoplasia, postoperative thoracic surgery, immune mediated hemolytic anemia, non-surgical portosystemic shunt and liver failure. Sex, age, and weight did not differ significantly between groups. Group C had a mean age of 8,5 years and 25,1 kg in weight. Group S had a mean age of 7 years in age and 30,8 kg in weight. An increase in %FO was associated with a slightly higher risk of death. The dogs in group C developed significantly higher %FO than the dogs in group S. Critically ill dogs were catheterized longer, received more fluid and stayed longer at the hospital than the stable dogs. Group C got on average 114,9 ml/kg/h while group S got 59,3 ml/kg/h of intravenous fluid. Risk factors identified in this study are listed in table 5. In the end, 10 dogs died, 8 of them had % FO greater than 12% and 2 had less than 12%FO. All the dogs that died were from group C or the critically ill dogs. This study concluded that critically ill dogs had a higher risk of fluid overload during hospitalization and that there was some association between %FO, illness severity and mortality.

Article 2

The second article aimed to describe patient characteristics, treatment and outcome in male cats with urethral obstruction and FO, and to determine risk factors for the development of FO. This study was a retrospective case-control study that looked at medical records of male cats admitted into the hospital in the years 2002 to 2012 trying to find patients with urethral obstructions that developed respiratory distress after fluid overload. Data of medical history, age, weight and body condition score prior to admission was collected, and records of heart rate, thoracic auscultation and blood pressure at admission. Treatment information including fluid type, rate, volume input and output, aspects surrounding FO, clinical signs, outcome and length of hospitalization were also recorded. Initially, 26 cats were identified from the medical record search. Fifteen of those cats were excluded from the study for the following reasons: FO but without respiratory distress, treatment at a different veterinary clinic prior to referral and cats with incomplete medical records. The included 11 cats were treated with IV fluids and had a urethral catheter placed and connected to a sterile urinary collection system for monitoring urine output. All 11 cats developed FO. In the present study, they compared their results to 51 control urinary obstruction cats without FO. Respiratory distress secondary to FO was categorized into either pleural effusion or pulmonary edema. None of the cats had known heart disease. At presentation, the median heart rate was 165/min with the range from 80 - 240/min in the cats who developed FO. The median heart rate in the control group was 200/min. The heart rate was significantly lower in cats that developed FO. A heart murmur was auscultated in 1 of the 11 cats at hospital admission; an additional 5 cats developed a heart murmur during hospitalization. During hospitalization, 10 of 11 cats developed a gallop heart sound and 1 cat developed a cardiac dysrhythmia characterized by ECG as ventricular tachycardia and atrial fibrillation. Initial intravenous isotonic crystalloid fluid boluses were administered in 7 cats that went on to develop FO. The median age of the cats with FO was 6 years and the median age for the control cats was 5 years, which did not make a significant difference in the development of FO. The median volume administered was 18.8 mL/kg of an isotonic crystalloid; 3 cats received Normosol-Rd and 4 cats received Plasmalyte. The initial intravenous fluid rate following urethral catheter placement in the 11 cats that went on to develop FO ranged from 3 to 20 mL/kg/h of an isotonic crystalloid. Presumed FO was diagnosed using thoracic radiographs in 8 cats, thoracic ultrasound in 2 cats, and positive thoracocentesis in 1 cat. Pleural effusion was diagnosed in 8 cats, of which 3 cats required therapeutic thoracentesis. Pulmonary edema was diagnosed in 7 cats, and 4 of these cats had

both pleural effusion and pulmonary edema. The median time from presentation to a diagnosis of FO was 39 hours (range 12.5 – 80 h). All blood work that was done was performed on heparinized whole blood. Whole blood sodium concentration was significantly lower in cats that went on to develop FO (P =0.017). Cats that received an initial IV fluid bolus were 5.1 times more likely to develop FO (95% CI, 1.3–20, P =0.014), 9 cats received a bolus. The development of a heart murmur during hospitalization was associated with the development of FO. The study also found an association between cats that developed FO and cats with congestive heart failure. Cats that developed a murmur during hospitalization were 4.5 times more likely to develop FO and cats that developed a gallop during hospitalization were 75 times more likely to develop FO. There were no significant differences in age, body weight, respiratory rate or the number of previous urinary obstructions between the cases and control cats. No cats were euthanized or died as a direct result of FO. This study was the first study to document the diagnosis and treatment of respiratory distress secondary to presumed fluid overload in cats. Though they conducted a risk factor analysis the study concluded that the incidence of fluid overload as a complication of treatment was unknown due to the possibility of other cats with fluid overload not being diagnosed or fluid overload not being recorded in a way that would show up during their medical record search.

Article 3

The third article focused on the incidence of hospital-acquired anemia as a side effect of fluid therapy among dogs and cats and identifying possible risk factors. This was a prospective observational study looking at patients from 2014 to 2015 without control groups. The data recorded from this study was body weight, diagnosis, medications and treatments, fluids administered, packed cell volume (PCV) and blood sample volume. The study assessed potential risk factors and came to the conclusion that cats had a higher chance than dogs of getting hospital-acquired anemia and that administration of higher volumes of crystalloid fluids was one of the associated risk factors. In the present study, 194 animals were admitted but 124 were excluded due to euthanasia, discharge or death in the first 48 hours. Six were excluded due to having received transfusion within the first 24 hours and 11 were excluded due to anemia at initial examination. The remaining 56 patients, 46 dogs and 10 cats were included. Upon arrival, a blood sample was collected from all patients and PCV measured. Anemia was diagnosed if the PCV was below a cut-off value of 39% in dogs and 28% in cats.

Cats did not have a higher odds of developing hospital-acquired anemia than dogs did. Sex was not significantly associated with the development of anemia. Bodyweight was not significantly associated with the development of hospital-acquired anemia. Dogs' median weight was 14,5 kg and 4,1 kg for cats. Sex or age did not affect the development of hospitals - acquired anemia and the median age was 6 years for patients that did develop hospital-acquired anemia and 6,15 years for those that did not. Administration of higher volumes of crystalloid fluids was associated with higher odds of developing hospital-acquired anemia. Surgery did affect the development of the hospital-acquired anemia. The types of surgery included cardiac, liver, orthopaedic, craniofacial and urologic surgeries. Of the 24 patients that underwent surgery, 15 became anemic while hospitalized. Of the 32 patients that did not have surgery, 12 developed hospital-acquired anemia. Only one of the 15 surgical patients that developed anemia developed it prior to the time of surgery. Out of 56 animals, 27 developed hospital-acquired anemia. 19 of the 27 animals had developed anemia within the first 24 hours, 24 of 27 within the first 48 hours and 27 within the first 72 hours.

Table 4. Overview of included articles.

Title	Retrospective evaluation of fluid overload and relationship to outcome in critically ill dogs **(Article 1)**	Retrospective evaluation of and risk factor analysis for presumed fluid overload in cats with urethral obstruction 11 cases 2000-2012 **(Article 2)**	Incidence of hospital-acquired anemia in hospitalized dogs and cats **(Article 3)**
Reference	(Cavanagh et al., 2016)	(Ostroski et al., 2017)	(Hiratzka et al., 2018)
Location of study	Colorado State University Veterinary Teaching Hospital, USA	Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania, USA	Fox Valley Animal Referral Center Wisconsin, USA
Study design	An observational, case-control study	Retrospective case-control study	Prospective, observational study.
Study population	34 critically ill dog 15 control dogs	11 cats with FO 51 cats without FO	46 dogs 10 cats no control group

Table 5. Overview of fluid therapy risk factors identified in the three included studies

Risk factors	Article 1	Article 2	Article 3
Being critically ill (Cats & dogs)	X	**X**	X
Development of heart murmur or gallop heart sound (Cats)		**X**	
Low whole blood sodium concentration (Cats)		**X**	
Undergoing surgery (Cats & dogs)			X
High doses of fluids (Cats & dogs)	X	**X**	X

Discussion

Interpretation of results

In the present systematic literature study concerning risk factors of crystalloid fluid treatment in dogs and cats three articles were included. The following risk factors for developing side effects of fluid therapy were identified; being critically ill, the development of heart murmur or gallop sound, having low whole blood sodium concentration, undergoing surgery and receiving high doses of fluids.

All included articles identified being critically ill as a risk factor for the development of FO. A higher association between being critically ill and mortality was observed compared to %FO and mortality (Cavanagh et al., 2016). The authors of the study debate that critically ill patients usually stay at the hospital for longer periods of time and get higher volumes of fluids, further increasing the risk of FO (Cavanagh et al., 2016). Veterinary guidelines for fluid therapy states that critically ill patients, in general, have a higher risk of developing side effects from fluid therapy (Byers, 2017; Davis et al., 2013). Literature from human medicine

addresses that fluid therapy can be in critical sick human patients is challenging. Critically ill patients have respiratory, cardiovascular and neurological issues that can result in electrolyte abnormalities, hypothermia, sepsis, metabolic derangements, shock, multi-organ failure and eventually death (Bennett et al., 2015). Shock is one of the most common conditions in critical patients and it requires immediate intervention with fluid therapy (Bennett et al., 2015; Finfer et al., 2018). In human medicine, trying to give sufficient fluids while avoiding complications without having a good diagnostic marker to predict response to therapy in critically ill patients is one of the current challenges (Aber et al., 2002; Lyu & Murphy, 2014; Perner et al., 2019). In our opinion, the same challenges also exist in veterinary medicine, as there are large similarities in the physiology between the species and the fact that all three articles found being critically ill a risk factor.

Receiving fluid boluses might be a risk factor for developing FO in cats however the affected cats developed FO hours or days after treatment, thus the association remains uncertain (Ostroski et al., 2017). Veterinary guidelines for fluid therapy also discussed a connection between bolus administration and electrolyte disorders, claiming that it could cause a rapid change in electrolyte concentrations (Fantoni & Shih, 2017). In human medicine, the efficacy and safety of fluid bolus administration are questioned due to an increased risk of a positive fluid balance, cardiovascular collapse, endothelial disruption and mortality (Glassford et al., 2014; Myburgh, 2015). However, in multiple studies fluid bolus was given as part of liberal fluid therapy, meaning that complications could be due to aggressive fluid therapy as a whole and not just bolus administration (Bouchard et al., 2009; Grams et al., 2011; Wiedemann et al., 2006). Research on the safety of fluid boluses are also affected by an unclear definition, the fluid bolus is when iv fluids are rapidly administered in discrete boluses, but according to human literature, there is no consensus on what classifies as a discrete bolus (Glassford et al., 2014). Therefore, we came to the conclusion that there is not sufficient data from neither veterinary nor human medicine to fully make an association between fluid bolus administration and FO.

Higher volumes of crystalloid fluid administration gave a higher risk of FO (Cavanagh et al., 2016). Veterinary guidelines for fluid therapy acknowledge that aggressive fluid therapy is a risk factor, associating it to FO, worsening of kidney function or lung injuries, edemas, heart failure and electrolyte disturbances (Driessen & Brainard, 2006; Fantoni & Shih, 2017;

Langston, 2017; Rozanski & Lynch, 2017; Thomovsky et al., 2016). Multiple human articles have also studied the relationship between fluid therapy and FO coming to similar conclusions and indicating that restrictive fluid therapy results in lower fluid balance, improved oxygenation and pulmonary function (Boehm & Menke, 2021; Claure-Del Granado & Mehta, 2016; Kassim & Esmat, 2016). An increase in the volume of crystalloid fluids administered was also associated with an increase in the odds of developing iatrogenic anemia (Hiratzka et al., 2018). In human medicine hemodilution caused by fluid resuscitation is a common condition (Paydar et al., 2014; Tsui et al., 2010). On the other hand, the association between aggressive fluid therapy and the worsening of anemia was only briefly mentioned in veterinary guidelines, particularly in association with hemorrhage and kidney disease (Langston, 2017). There did not seem to be much research done on small animals however we did find a study on cats that confirmed that hemodilution due to fluid therapy could lead to anemia (Balakrishnan et al., 2016). As well as a study was done on rats that also deduced that high amounts of fluids affected hemodilution and coagulability (Nishi et al., 2013). These studies reinforce aggressive fluid therapy as a risk factor for hemodilution and anemia.

Patients undergoing surgery were associated with the development of iatrogenic anemia with possible causes being underlying diseases, surgical technique, general anaesthesia or perioperative medications (Hiratzka et al., 2018). In a similar study on cats and dogs, an association between surgical intervention and the development of iatrogenic anemia was established, the hypothesis was that perioperative hemorrhage and fluid resuscitation could cause anemia (Lynch et al., 2016). In human medicine postoperative anemia is relatively common in those who undergo major surgery (Bolliger et al., 2010; Desai et al., 2018). Fluid therapy tends to be the initial treatment to stabilize circulation, this can worsen the situation because of hemodilution which can lead to anemia (Bolliger et al., 2010; Warner et al., 2020). Veterinary guidelines for fluid therapy also indicate that anaesthesia is a risk factor for fluid therapy as it affects the body's hemostasis and sick patients that are anaesthetized are more likely to experience altered fluid balance (Fantoni & Shih, 2017). Based on this information and our findings on hemodilution, although the clinical effects of this iatrogenic anemia have not been investigated it is highly likely that veterinary patients undergoing surgery would also have a higher risk of iatrogenic anemia as a side effect of fluid therapy.

An association between cats that developed FO and cats with congestive heart failures was found and 91% of the cats in the study that developed FO also developed a gallop murmur

(Ostroski et al., 2017). The authors also discuss that the development of gallop heart sounds could be due to underlying heart disease, aggressive fluid therapy affecting blood's rheological characteristics or the development of occult FO. In veterinary guidelines for fluid therapy heart failure or heart disease is acknowledged as an important risk factor. Patients with heart issues have a bad tolerance for sudden increases in intravascular volume, fluid therapy can lead to heart failure and gives a higher risk of FO (Driessen & Brainard, 2006; Thomovsky et al., 2016). Veterinary guidelines of fluid therapy also state that cats are prone to suffer from an inappropriate fluid plan, since they are less tolerant to aggressive fluid therapy due to occult cardiac disease, have a lower metabolic rate and a smaller blood volume (Tello & Perez-Freytes, 2017). In human medicine heart murmur is not considered a direct risk factor of fluid therapy however, heart murmurs are often associated with heart failure which is a risk factor for FO in humans (Shotan et al., 2005). In cats that had heart murmurs before commencing treatment did not have an increased risk of FO (Ostroski et al., 2017). We hypothesize that cats without heart murmurs before treatment may have received more aggressive fluid therapy than those with known heart murmurs. A review article on veterinary fluid therapy indicates that while fluid therapy should be carefully administered and monitored, the development of heart murmur alone does not mean fluid therapy should be limited when treating hypovolemia or dehydration (Rozanski & Lynch, 2017). In our opinion, more research is needed to determine if heart murmurs are a direct risk factor to FO, but it is obvious that heart murmurs are a risk for underlying heart disease.

In cats, lower blood sodium concentration (hyponatremia) upon arrival has been associated with the development of FO (Ostroski et al., 2017). Veterinary guidelines for fluid therapy also present pre-existing electrolyte disturbances, like hyponatremia, as risk factors. Fluid therapy can either dilute or add electrolytes to the body thus having the possibility to exacerbate existing disturbances. Electrolyte abnormalities are among other things associated with neurological signs, edemas, arrhythmias, hypotension, decreased cardiac output, carbohydrate intolerance, anorexia, exacerbation of lethargy, and gastrointestinal hypomotility (Boysen, 2008; Fantoni & Shih, 2017; Tello & Perez-Freytes, 2017). In a lot of cases, it's therefore advised that fluid administration should be closely monitored, and electrolyte disorders and dehydration corrected gradually (Langston, 2017).

One important aspect that was not found to be a risk factor in the articles we analyzed but is mentioned in veterinary fluid therapy guidelines is age. In human research, both younger

children and the elderly are at higher risks of unwanted side effects from fluid therapy (Chisti et al., 2016; El-Sharkawy et al., 2013; Hawkins, 2003). In veterinary medicine, kittens and puppies are believed to be high-risk patients with regards to fluid therapy. Young patients can get severely dehydrated and hypovolemic because of their size and physiology; a larger fluid loss from more permeable skin, larger surface area/ bodyweight ratio and an immature kidney that cannot concentrate urine properly and therefore often need fluid therapy of higher doses when sick (Horster & Valtin, 1971; Kleinman & Lubbe, 1972; Lee & Cohn, 2017). It is also difficult to monitor and assess fluid status in small patients and fluid therapy can cause a fall in their temperature (Lee & Cohn, 2017). Weight was not found to be a risk factor in our study, however veterinary guidelines for fluid therapy states that weight can affect the assessment of fluid therapy needs and consists of a risk factor for incorrect calculation (Byers, 2017). More research is needed on whether age and weight are risk factors of fluid therapy in veterinary medicine.

It's difficult to compare dogs to cats from our findings, as there is a difference in study population numbers and not enough data. Most of the study population were dogs. Most of the risk factors were also applicable to both dogs and cats except for the development of heart murmur or gallop sound and having low whole blood sodium concentration, which was only identified in cats. However, while article 3 did not find a difference in the development of anemia due to fluid therapy, we have been able to find a veterinary study that suggests cats are more likely to develop anemia from blood loss due to their small size and overall smaller blood volume (Balakrishnan et al., 2016). Research with a larger or more even study population is needed to properly compare the species.

Risk factors provided by fluid therapy guidelines

The results we found do somewhat agree with the general consensus of which risk factors of fluid therapy exist. Patients with pulmonary disease, renal disease and shock are also believed to be common high-risk patients (Boysen, 2008; Davis et al., 2013). Pulmonary injuries or diseases can be made exponentially worse from fluid therapy (Rozanski & Lynch, 2017). In normotensive patients, it is advised to minimize fluid therapy (Driessen & Brainard, 2006). Renal diseases or renal injuries also have a big effect on the results of fluid therapy as a decrease in renal function can exacerbate electrolyte dysfunctions and disturbances in the water balance (Boysen, 2008; Fantoni & Shih, 2017).

Other patients at risk include those with anorexia, vomiting, diarrhea, severe dehydration, traumatic brain injury, hemorrhage, vasculitis and endocrine disorders (Boysen, 2008; Davis et al., 2013; Fantoni & Shih, 2017). Patients with severe dehydration can suffer more from sudden changes to their fluid balance. Ongoing fluid losses through vomiting and diarrhea are hard to calculate, making it difficult to monitor therapy and to properly correct dehydration (Boysen, 2008; Fantoni & Shih, 2017). These types of fluid losses can also further worsen electrolyte disorders (Fantoni & Shih, 2017; Langston, 2017). Endocrine disorder emergencies affect fluid loss, electrolyte and acid-base balance, kidney function and blood pressure (Boysen, 2008; Fantoni & Shih, 2017). Certain medications can also be risk factors for side effects, for example, mannitol can worsen the effect of dehydration in hypovolemic patients or pulmonary edema in patients with fluid overload (Langston, 2017).

Why these additional risks were not picked up by our study can partially be due to the limited amount of research articles we analyzed and the limited study population. It is also important to remember that some of these risk factors have been adopted from human medicine and that further research on small animals may be needed to assess whether or not these risk factors are relevant to dogs and cats.

Article weaknesses

Article 1 had several limitations due to its retrospective design. This study was limited to dogs with indwelling urinary catheters which introduced a selection bias. Since body weight was not consistently recorded it could not be used as an additional serial measurement to corroborate the presence of fluid overload. They therefore used a formula for calculating %FO in children that did not require obtaining weight daily. Initial percent dehydration was subtracted from the calculated %FO in order to account for the appropriate interstitial fluid replacement, this percent dehydration was estimated by different clinicians and that may have affected the %FO calculations in both groups.

Article 2 excluded nine cats with urinary obstruction and presumptive fluid overload but were not found to be in respiratory distress which may have biased their results. We cannot completely rule out the possibility of occult FO in the control cats and therefore the true incidence of FO as a complication of treatment of urinary obstruction is unknown. This study

found out that the development of heart murmur or gallop sound was a risk factor but five of the cats did not undergo echocardiography and therefore it cannot be assumed that underlying heart disease is the cause of FO in all animals.

Article 3 had a small sample size and short duration of hospitalization, < 72 hours, compared to similar human studies and they did not calculate illness severity scores. In human medicine patients with higher illness severity scores have more severe anemia and not measuring could have affected the conclusion of this study. They did not find cats to have a higher risk of developing hospital-acquired anemia in contrast to results of a multicenter study that indicate that cats have a higher risk of developing hospital-acquired anemia compared to dogs. (Lynch et al., 2016) That study however investigated the effect of blood transfusion and not intravenous fluid therapy with crystalloid solutions. Most of the patients in article 3 were dogs and therefore low statistical power likely affected their results with regards to cats. This study also excluded animals if they had to be euthanized or died which could affect the results and makes the article slightly weaker in comparison to the two others.

Literature search weaknesses

The findings of our study are limited as only three articles were deemed relevant to our study. Two possible reasons for this are the way we conducted our search or a lack of research articles on the subject. There is a chance we would have found more articles had we included various side effects as keywords. It could also have been beneficial to conduct a search for individual side effects and risk factors and then compare the results. It is possible there are more studies in different databases or in other languages. We also considered that perhaps the limited time period (2000 - 2020) was an issue, because of this we did attempt a search without a set time frame, but no additional articles that followed our criteria from before 2000 were found.

Multiple articles from veterinary medicine commented on the lack of research done on cats and dogs and also point out that a substantial amount of current knowledge comes from human medicine literature (Kristina, 2020; Thomovsky et al., 2016). Both the veterinary fluid therapy guidelines and the articles analyzed mostly used literature from human medicine as background and references. Veterinary fluid therapy is a less developed field, research so far

has seemingly focused on the effect of different fluid strategies and fluid solutions in small animals. We believe that the biggest limitation of our study is that there has not been enough research on the specifics of fluid therapy in veterinary medicine.

Clinical significance

After our search for literature, we realized that there is not much to be found on this topic that relates to the veterinary field. An online survey on fluid therapy in small animals found that little is known about the current fluid therapy practices in veterinary medicine (Hopper et al., 2018). Research on fluid therapy in veterinary patients to decide the most effective monitoring to assess response, especially in anaesthetized patients, is clearly needed. We can speculate on why there may not be much research done on the subject. It's possible that research done in human medicine has given enough information about the risk factors of fluid therapy and that this information is applicable to dogs and cats.

Furthermore, a lot of the references in our three veterinary studies concerned human medicine. Fluid therapy may be one of the subjects in veterinary medicine where we operate on the assumption that if something can cause a problem for humans it most likely will cause problems for animals as well. In our opinion, the water balance physiology is similar in animals and humans and that could be the reason veterinarians use human medicine knowledge. Because of this, it could be ethically ambiguous to conduct studies on this subject, as it would perhaps require experiments on animals with known risk factors, and some may view it as bad animal welfare or unnecessary animal research. There are of course ways to research this without putting dogs or cats through compromising clinical studies, for example, retrospective studies on animals that have already been through treatment. New treatments may be necessary both for the interest of the individual animal and for the advancement of veterinary science.

Conclusion

In the present study, we aimed to identify the risk factors of crystalloid fluid therapy in dogs and cats. The risk factors we identified included: being critically ill, the development of heart murmur or gallop sound, having low whole blood sodium concentration, patients undergoing

surgery and getting high doses of fluids. In our opinion, our systematic literature study was to some degree insufficient in answering the question “what are the risk factors of crystalloid fluid therapy in dogs and cats? “. Although some suspected risk factors were identified, our study failed to include other established risk factors identified in veterinary guidelines. We believe more research on this exact topic in veterinary medicine is needed. With increased knowledge on the subject, we will be able to better monitor and care for patients receiving fluid therapy and hopefully avoid or faster detect adverse side effects.

Thanks to contributors

We would like to use the opportunity to thank our supervisors Runa and Marit for their patience, help and useful feedback.

Sammendrag

Tittel: Risikofaktorer for å utvikle bivirkninger ved krystalloid væskebehandling hos hund og katt

Forfatter: Beatriz Bergolla Hidalgo, Birna Sólbjört Jónsdóttir

Veiledere: Runa Rørtveit, institutt for prekliniske fag og patologi, and Marit Jørgensen Bakke, institutt for parakliniske fag

Bakgrunn og Mål: Det er en kontinuerlig utveksling av væske og elektrolytter mellom de ulike kroppsvæske avdelingene og forstyrrelser i væskebalansen kan være dødelige. Krystalloide væsker krysser den intravaskulære barrieren og blir ofte brukt til væskebehandling i veterinærmedisin. Væskebehandling stabiliserer og korrigerer væske, elektrolytt og syre-base balansen, men kan være forbundet med negative bivirkninger og det finnes ulike risikofaktorer som kan påvirke resultatene av væskebehandling. I denne systematiske litteraturstudien ønsket vi å få mer kunnskap om risikofaktorene ved krystalloid væskebehandling hos hund og katt.

Materialer og Metoder: Vi søkte tre ulike databaser etter fagfellevurderte artikler skrevet på engelsk i tidsperioden 2000-2020. Søkeordene som ble brukt var hund, katt, væsketerapi, ivvæske, intravenøs, risiko og risikofaktorer. Dette søket ga oss tre artikler å analysere.

Resultater: Å være kritisk syk, få høye doser væskebehandling og å gjennomgå kirurgi ble identifisert som risikofaktorer for bivirkninger av væskebehandling i både hunder og katter. Mens utviklingen av hjertemusling eller bilyd og å være hyponatremisk før behandling ble identifisert som risikofaktorer hos katter.

Konklusjon: Det er få artikler som har studert risikofaktorene for væsketerapi hos hund og katt og de fleste anbefalinger i veterinærmedisin er basert på forskning fra humant medisinsk. Vi mener at mer forskning på hund og katt vil være gunstig for å kunne forbedre væskebehandling i veterinær feltet.

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