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Evaluation of Albumin Administration in Canine Patients: Necessity, Risks and Current Perspectives

Hyun-Jung Han*

Department of Veterinary Emergency and Critical Care, College of Veterinary Medicine, Konkuk University, Seoul, Korea

Mini Review

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***For Correspondence:** Hyun-Jung Han, Department of Veterinary Emergency and Critical Care, College of Veterinary Medicine, Konkuk University, Seoul, Korea

E-mail: ab1234@konkuk.ac.kr

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ABSTRACT

Albumin plays a major role in maintaining physiological functions in dogs, serving as a carrier protein and contributing to colloid osmotic pressure regulation. In veterinary medicine, albumin administration is essential for managing hypoalbuminemia in critically ill dogs. While Canine Serum Albumin (CSA) is the preferred choice to moderate hypersensitivity risks, constraints in availability and cost often lead to the use of heterologous albumins like human serum albumin and bovine serum albumin. However, the use of heterologous albumins poses significant challenges, including the potential for fatal hypersensitivity reactions. This review focus on the necessity and application of albumin in dogs, critical issues associated with heterologous albumin administration and the current status of CSA use. Future strategies should focus on enhancing the availability of CSA and exploring safer alternatives to ensure effective albumin therapy in canine patients.

Keywords: Albumin therapy; Canine Serum Albumin (CSA); Critically ill dogs; Heterologous albumins; Hypersensitivity

INTRODUCTION

Albumin is the primary protein that constitutes plasma. It maintains colloid osmotic pressure, regulates acid-base balance, preserves endothelial integrity and functions as a carrier protein for transporting drugs, nutrients, fatty acids, bilirubin, hormones and iron [1,2].

In the veterinary field, particularly for dogs, albumin is clinically utilized for critically ill patients with hypoalbuminemia and is sometimes added as a stabilizer to preservation or reaction solutions. When clinical administration of albumin is necessary in dogs, the ideal choice is Canine

Serum Albumin (CSA) extracted from dogs to reduce the risk of hypersensitivity reactions. However, due to several limitations, including the availability of commercially developed CSA products and financial constraints, heterologous albumin, such as Human Serum Albumin (HSA) or Bovine Serum Albumin (BSA), is often used instead. The use of heterologous albumin demands caution due to potential severe side effects, including hypersensitivity reactions and ethical concerns, particularly with HSA.

LITERATURE REVIEW

This article provides a critical review of the use of heterologous albumin in the veterinary field, focusing on dogs, addressing the following aspects:

- The necessity and application of albumin in dogs.
- The critical issues associated with heterologous albumin administration to dogs.
- The current status of CSA use and future strategies.

Necessity and application of albumin in dogs

The primary reason for administering albumin to dogs is to correct hypoalbuminemia resulting from critical conditions such as septic peritonitis, protein-losing enteropathy and liver diseases [2,3]. Dogs may also be exposed to albumin indirectly through the administration of vaccines or lyophilized products that contain albumin as a stabilizer [4-10]. Hypoalbuminemia can lead to serious complications, including reduced oncotic pressure, delayed wound healing, decreased transport capacity for drugs and hormones, disrupted acid-base balance and ultimately increased morbidity and mortality in critically ill dogs [11]. Human studies suggest that decreased serum albumin levels significantly affect mortality rates; a decrease of 0.25 g/dL can raise mortality by 25%-50% and a decrease of 10 g/dL can increase mortality by 137% [12,13].

Plasma products containing albumin, such as fresh frozen plasma or cryo-poor plasma, have demonstrated efficacy in raising Colloid Oncotic Pressure (COP) and albumin concentration [2]. However, factors such as the large plasma volume needed for effective albumin supplementation, blood product availability and financial limitations prevent these from being widely feasible options in canine patients [11]. Synthetic colloids, which are more economical and accessible than plasma products, have been utilized for oncotic support in hypoalbuminemic patients. Nonetheless, they have been associated with detrimental side effects, including acute kidney injury, coagulopathy and even death when administered to critically ill patients [14-18]. Moreover, synthetic colloids fail to perform other critical functions of albumin, such as drug delivery and acid-base buffering, aside from maintaining oncotic pressure. As a result, albumin supplementation remains necessary for restoring albumin functions in dogs with hypoalbuminemia.

Additionally, dogs may encounter albumin through products that include it as a buffer, such as vaccines and other lyophilized biological products. BSA is particularly prevalent in canine vaccines, where it supports cell growth and is often present after manufacturing [5]. During lyophilization, albumin plays an important role as it increases the glass transition temperature, thereby enhancing the survival of lyophilized cells [6-8]. BSA is more cost-effective and easier to obtain than albumin from other species, making it the preferred choice for buffer incorporation in various biological products for both humans and animals.

Given the diverse clinical scenarios necessitating albumin administration in dogs, either intentionally or inadvertently, it is vital to comprehend both the indications for use and the associated risks thoroughly.

Critical issues associated with heterologous albumin administration to dogs

Currently, the types of albumin administered to dogs include HSA, CSA and BSA. These proteins share considerable structural and sequence similarity, with approximately 83%-88% structural homology and 75%-79% sequence homology [19-23]. Notably, BSA and HSA exhibit similarities in solvent accessibility and drug binding affinity, which has led to BSA being utilized as an alternative to HSA in various pharmacokinetic studies and ligand-binding experiments [1]. Moreover, BSA is frequently utilized in pediatric vaccines, artificial insemination, tissue adhesives, hemostatic agents and anticancer nano-delivery systems [24-28]. In contrast, CSA displays greater dynamic flexibility compared to the other two albumins. Given that the sizes and environments of CSA drug sites differ from those of BSA and HSA, further research is warranted to explore the binding affinity of existing ligands to CSA [1].

Despite the structural similarities among these albumins, their interchangeability in clinical settings remains a subject of ongoing inquiry, with evaluations being made across both veterinary and human medical fields as substitutes for one another. Among these options, CSA, specifically developed as lyophilized, canine-specific concentrated albumin has been in use for approximately 10 years; however, its availability is limited to regions like the United States of America and Canada, while it remains inaccessible in many areas, including Asia. In regions where CSA is unavailable, HSA is still frequently used for albumin transfusions in dogs with hypoalbuminemia. The most significant concern regarding HSA transfusions in dogs pertains to the high risk of severe hypersensitivity reactions, including anaphylactic shock, vasculitis and glomerulonephritis [29-32]. Fortunately, prior veterinary studies indicate that critical reactions to HSA have been infrequent among critically ill dogs compared to healthy individuals. Among healthy dogs given HSA, hypersensitivity reactions occurred in two of nine dogs, six of six dogs and one of two dogs, with notable cases resulting in protein-losing nephropathy or severe systemic vasculitis leading to death [31-33]. In contrast, in critically ill dogs, HSA administration significantly improved serum albumin levels, COP and blood pressure without severe side effects; only two of 64 dogs displayed mild facial edema and three of 73 dogs exhibited mild signs of delayed hypersensitivity [34-40]. Although the reasoning behind the discrepancy in hypersensitivity reactions between critically ill and healthy dogs remains uncertain, it has been posited that the impaired immune response and attenuated antigenic effects associated with heterologous albumin use could play a role in moderate severity and occurrence rates in critically ill canines [11]. Nevertheless, reports of fatal complications such as vasculitis, acute glomerulonephritis and even death persist in critically ill dogs, necessitating careful consideration of these potential risks [29,30].

In terms of BSA, due to its cost-effectiveness and accessibility, research has been conducted to ascertain its viability as an albumin transfusion option for dogs. However, mild to severe hypersensitivity reactions, including anaphylaxis, were recorded in seven of ten dogs, indicating a higher risk than that associated with HSA administration, which ultimately excluded BSA as a viable option for canine albumin transfusions [12,41].

BSA has been frequently incorporated into canine vaccines and lyophilized biological products, with reported risks of inducing severe hypersensitivity reactions post-administration [4,9,10,42]. Most canine vaccines, barring recombinant Lyme disease vaccines, contain significant amounts of BSA, contributing to the risk of fatal hypersensitivity reactions [9,10]. According to a study from Japan, both rabies and non-rabies canine vaccines contain varying concentrations of BSA, with non-rabies vaccines holding higher quantities (61.6 µg/dose to 3,678 µg/dose) leading to increased hypersensitivity risk, while rabies vaccines typically contain lower amounts (0.1 µg/dose to 16.6 µg/dose), resulting in fewer reported reactions [9].

In studies examining lyophilized platelet products for dogs, BSA has been deemed an inappropriate component due to its immunogenicity stemming from species differences [4]. In assessing buffer efficacy and safety in lyophilized platelets, hypersensitivity reactions occurred in four out of five dogs when BSA was administered *via* intradermal and intravenously, indicating reactions including skin manifestations, gastrointestinal sign and anaphylaxis [4]. Additionally, exposure to bovine albumin through food sources (e.g., milk or beef) poses risks, as cross-reactivity may induce fatal hypersensitivity reactions following BSA administration [43]. Human studies have reported that patients with cow's milk allergies exhibited hypersensitivity reactions following vaccinations containing BSA [28].

Consequently, despite the high structural similarity and functional capabilities of heterologous albumins, clinical use of HSA and BSA in dogs presents significant challenges, given the potential for severe adverse reactions.

Current status of CSA use and future strategies

Presently, there is no definitive solution to check the immunogenicity of heterologous albumins, making CSA the most promising option for albumin administration while minimizing hypersensitivity risks. Commercially available CSA comprises 98% lyophilized canine albumin derived from plasma and is devoid of preservatives, though it may contain residual leukocytes or cytokines. Prior veterinary studies have reported no significant side effects, including acute or delayed hypersensitivity reactions, following lyophilized CSA administration in critically ill dogs or even healthy dogs, with the exception being a recent large population study [44-46]. In this recent study, transfusion reactions were identified in 13 of 64 administrations of lyophilized CSA, primarily manifesting as dyspnea or febrile non-hemolytic transfusion reactions, with a fatality rate of 15.4%; however, these events did not impact the duration of hospitalization or treatment outcomes [2]. Notably, the observed transfusion reactions did not resemble type I or III hypersensitivity reactions associated with heterologous albumin and are instead thought to stem from residual leukocytes or cytokines in CSA.

While CSA is generally viewed as safer and more effective than heterologous alternatives without any documented fatal hypersensitivity reactions, its commercialization has been limited by regional and economic challenges. Outside of the United States of America and Canada, accessing lyophilized CSA for transfusions remains difficult and replacing BSA in canine vaccines or lyophilized products with CSA incurs additional costs. To address these commercialization challenges, our laboratory is actively working to manufacture lyophilized CSA that can be provided Tanto domestically as well as in Asia, drawing from canine blood donation centers. Moreover, apart from BSA, which has triggered hypersensitivity reactions upon use in lyophilized platelets, alternative buffer systems and methodologies are currently under investigation. Through these initiatives, we aimed to facilitate safer and more effective albumin administration in dogs by increasing the availability of CSA and diminishing reliance on heterologous albumins.

CONCLUSION

Overall, CSA is perceived as a safer and more effective species-specific albumin to heterologous albumins regarding hypersensitivity risks. However, it has not been widely commercialized due to regional, economic and accessibility factors. In areas excluding the USA and Canada, acquiring lyophilized CSA for albumin transfusion remains problematic, while cost concerns limit the replacement of BSA in canine vaccines and lyophilized products. Our laboratory is making strides to produce domestically available lyophilized CSA, catering to the Asian market, alongside exploring alternatives to BSA that have previously evoked hypersensitivity. With these active efforts, the

goal is to promote safer and more effective albumin administration for canine patients by enhancing CSA's clinical accessibility while minimizing the need for heterologous albumin.

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