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Review Article

Albumin Infusion Therapy in Critical Patients

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Abstract

Human albumin has been the area of interests and research for the last 65 years. A major advance in our understanding of albumin has been achieved as complete gene sequence and the location of mutations of albumin was unfolded. Clinical uses of albumin were first introduced during the Second World War when adequate plasma supply was not possible due to logistical complexities. In the 1950s, this protein was introduced for management of patients with liver cirrhosis however differing opinions exist amongst hepatologists. Critical illness causes changes in the rates of synthesis and degradation of albumin and this illness also alters the distribution of albumin protein between intravascular and extravascular spaces. The human albumin level which falls in early part of critical illness will not easily rise again until the recovery phase of that illness. Giving exogenous albumin to increase the intravascular albumin concentration during critical illness is beneficial, although the kinetics of albumin given intravenously will differ greatly between critically ill-patients and healthy individuals. This review aims to discuss current opinion, interest and clinical application of albumin infusion therapy and will inspect the role of albumin in health and critical illness.

Key words: *albumin, clinical uses of albumin, and albumin therapy in liver diseases.*

Introduction:

Albumin is most abundant plasma protein consisting of 55-60% of total serum protein. Albumin is a typical physiological buffer maintains 80% of the normal colloid oncotic pressure (COP) in healthy individuals due to its high molecular weight and higher concentration in plasma. It plays an important role in the regulation of tissue fluid distribution due its large extravascular collection, water-solubility and negative charge[1]. However, albumin is responsible for few others important biological functions, hence it should be treated as a drug and not just as a form of fluid used for resuscitation. The molecular structure of albumin is flexible and changes its shape readily with variations in environmental conditions and binds with ligands. Despite the flexibility of albumin molecules, once the bonds are broken down, the molecule can reinstate the bridges and recover its structure. Denaturation of albumin occurs only with dramatic and non-physiological changes in temperature, pH and the ionic or chemical environment[2]. Albumin binds many endogenous and exogenous compounds, including fatty acids, metal ions, pharmaceuticals, and metabolites, with implications for drug delivery and efficacy, detoxification, and antioxidant protection.[3] Albumin, with its multiple physiological effects of volume expansion, antioxidation and endothelial protection, would seem an ideal treatment solution for patients with in particularly liver cirrhosis and its complications. In critically ill-patients, the choosing optimal resuscitation fluid remains unidentified. Hence, future research study should focus on the potential beneficial role of albumin and the primary resuscitation fluid in critically ill-patients with cirrhosis may be re-evaluated.

Methods:

An extensive PubMed internet search was carried out up to 31 May 2018. Human albumin, clinical uses of albumin, and albumin in liver diseases were used as key information words for the internet search. Only original research work and systematic review articles were chosen from peer reviewed journals to evaluate and analyze pathophysiological, therapeutic and beneficial role of albumin. Only articles written in English were considered for writing this review.

Discussion:

a. Structure of albumin

Albumin consists of a single polypeptide chain of 585 amino acids with a molecular weight of 66,500 Dalton and the chain is characterized by the lack of carbohydrate moiety, a deficiency of tryptophan, methionine residues, and plenty of charged residues like lysine, arginine, glutamic acid and aspartic acid[4]. The X-ray crystallography image confirms a heart-shaped structure of albumin which is arranged in a series of alpha-helices, folded and held by seventeen disulphide bridges cross-linking cysteine residues and uniting the three domains[5]. Those disulphide bridges give enough strength to albumin and ease conformational changes in response to ligand binding whereas folding creates sub-domains of three adjacent alpha-helices in parallel. A pair of sub-domain faces each other to form domains. These can

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be seen as cylindrical structures with polar external walls and a hydrophobic middle center[6].

b. Pathophysiology of albumin

Albumin is mainly synthesized in polysomes of liver hepatocytes at the rate of 10-15 gram/day and released that in portal veins. Synthesis of albumin is a constant process regulated at both transcriptional and post-transcriptional levels as stimulated by the colloid osmotic pressure of the interstitial fluid rinses hepatocytes[1,7]. Albumin binds to a surface receptor called albondin, which is widely distributed in many capillary beds, except in the brain[8]. Degradation of albumin occurs in the liver and kidney, but the majority degradation takes place in the skin and muscle (the main locations of extravascular albumin)[9]. Altered or denatured albumin binds to endothelial cell surface receptors; following uptake into intracellular vesicles, fusion with lysosomes results in breakdown into free amino acids[10]. The partial degradation rate of albumin is 3.7% which parallels the rate of synthesis in health. As only little amount of albumin is reserved in hepatocytes, on demands, there is no reserve of albumin for release to fulfill the demands[1]. However, hepatocytes are able to synthesize 2-3 folds more albumin than normal production as required, provided there is an adequate amount of available messengerRNA [7]. Albumin will be synthesized only in a suitable nutritional, hormonal and osmotic environment. The COP of the interstitial fluid bathing the hepatocyte is the most important regulator of albumin synthesis. Each day, 120-145 gram of albumin is lost into the extravascular space. Most of this is returned into the circulation by lymphatic drainage[1]. Albumin is also lost into the intestinal tract, where digestion releases amino acids and peptides, which are reabsorbed. There is negligible urinary loss of albumin in healthy subjects[11]. Of the 70 kg of albumin that passes through the kidneys each day, only a few grams pass through the glomerular membrane. Nearly all of this is reabsorbed, and urinary loss is usually no more than 10-20 mg day.

c. Functions of albumin

The albumin molecules are easily able to bind and engulf different compounds within its structure due to its structural flexibility. For example, most strong bonds are medium-sized hydro-phobic organic anions, including long-chain fatty acids, bilirubin and haematin[6]. Other endogenous compounds that bind to albumin include bile acids, eicosanoids, copper, zinc, foliate and aquacobalamin. Albumin is also a secondary or tertiary transporter for a number of substances that have specific binding proteins, for example, steroids, including derivatives such as vitamin D and thyroxine[1]. Drug bindings robustly affect the release of bound drug to tissue sites, the metabolism and removal of the drug. There are various factors influencing drug-albumin interactions that turn relevant in critically ill-patients and one of the examples is renal failure[11]. In vitro investigation suggests antioxidant potential of albumin which is involved in scavenging of oxygen free radicals, which have been mixed up in the pathogenesis of inflammatory diseases[12]. It is also reported that albumin is an important source of sulfhydryl groups that bind with nitric oxide forming a stable S-nitrosothiol group in circulation and is thus protected from rapid degradation[13]. Albumin affects blood coagulation as it is supposed to exert a heparin-like action through enhancement of the neutralization of factor Xa by antithrombin-III because there is a similarity in structure of two molecules[14]. The albumin molecule serves as the transport vehicle for thyroid and steroid hormones, fatty acids, unconjugated bilirubin, and several drugs[15,16]. It has been proposed that serum albumin could be an independent predictor of mortality in clinical settings[17] and a low serum albumin concentration correlates with increased length of hospital stay and higher complication rates, such as ventilator dependency and new infection. Thus measuring daily serum albumin level can be a valuable tool in predicting the weaning capability of patients on mechanical ventilation. Non-survivors of critical illness have shown lower serum albumin concentrations than survivors, and their albumin concentrations decreased more rapidly in the first 24-48 hours[18].

d. Clinical uses of albumin

Large volume paracentesis (LVP) and albumin - Despite disagreement between clinicians for albumin infusion therapy in critical patients, published data strongly supports the use of albumin in the treatment or prevention of certain complications of liver cirrhosis. Like, LVP remains the only available treatment option for cirrhosis patients having refractory ascites[11,19]. LVP, however induced circulatory dysfunction and strategies to prevent post-LVP circulatory dysfunction have been attempted by infusing albumin or colloidal solutions or vasoconstrictors demonstrated significantly lower incidence of post-LVP circulatory dysfunction with albumin compared to each of the other treatment modalities.

Hepatic renal syndrome (HRS) and albumin - HRS is an alarming complication of advanced cirrhosis with development of renal failure in the absence of any identifiable causes of renal pathology. Systemic vasoconstrictors such as vasopressin analogues and α-adrenergic agonists have been used to treat HRS, with some success[20]. Albumin is traditionally considered to improve circulatory function in cirrhosis by expanding central blood volume and increasing cardiac output[21]. It is, therefore, conceivable that an improvement of renal function in patients with HRS treated with vasoconstrictors and albumin is due to the additive effects that the two compounds have on plasma expansion and peripheral arterial circulation.

Spontaneous bacterial peritonitis (SBP) and albumin - One third of patients with SBP, another common complication in patients with cirrhosis and ascites, develop renal dysfunction secondary to rapidly progressive impairment in systemic hemodynamic. The combination of antibiotics with albumin was recognized for the treatment of SBP[22].

Burn and albumin- It was proposed that albumin is not necessary for burns covering less than 15% of the body surface, but is essential from the start of treatment for patients with greater than 50% burns, hence burnt patients are a

specific group for whom albumin may have a beneficial role[23].

Therapeutic plasma exchange and albumin- In plasma exchange, patient's plasma is removed and a colloid solution is used as replacement fluid instead. 5% human albumin is preferred as a replacement fluid in many diseases in performing therapeutic apheresis. Albumin solutions are pasteurized to inactivate viruses, carry a very low risk of febrile and allergic reactions, and are convenient to store and administer[24].

e. Adverse effects of albumin

Like any other therapy, albumin is not free from untoward effects. Allergic reactions to albumin are not common but may happen from contaminants in the solution or polymers that are formed upon long-term storage. Hypersensitivity reactions may occur, with fever, chills, tremors, nausea, abdominal discomfort, malaise, headache, rubor, urticaria, dyspnoea, tachycardia, hypotension and/or collapse[25]. Therefore, injudicious use of albumin may cause fluid overload as plasma volume increases linearly with the dose of albumin. Viral transmission through albumin therapy is extremely unlikely as prolonged heat treatment is employed in its preparation process[26].

Conclusions:

Albumin, produced by plasma fractionation since 1941, has been widely used in clinical practice despite controversy, mainly for its intravascular volume expansion properties[1]. In the opinion of majority experts, long-term albumin infusion tends to produce a subjective feeling of "comfort" which is useful in improving patient's general conditions[27]. Some researchers claim that albumin supplement as parental nutrition may shorten hospital stay reducing the morbidity.[28] However, it is now evident that serum albumin is not a dependable indicator of nutritional status in critically ill-patients[29]. In terms of volume expansion therapy, albumin does not appear beneficial as compared to other colloidal solutions[1]. Dutch Cancer research group have shown that patients with peritoneal cancer undergoing prolonged surgery might benefit from albumin infusion therapy[30]. The role of albumin is being redefined given its properties beyond being simply a plasma expander, one example of this new role of albumin is molecular adsorbent re-circulating system (MARS)-albumin hemodialysis[31]. MARS, an artificial liver support using albumin as hemodialyser shows ability to remove toxins and pro-inflammatory stimuli, such as lipopolysaccharides, chemokines, lipid peroxidation end-products, xenobiotics and free hemoglobin, may have implications for limiting the inflammatory response. And MARS plus albumin has been used to treat liver dysfunction and failure also shown improvement in renal function, hemodynamic, and to reduce brain edema and hepatic encephalopathy[32]. Although, no conclusive benefit with regards to mortality in using albumin has not been demonstrated. But human albumin is considered a safe product as regards to transmission of pathogenic agents because it is subjected to a process of sterilization by pasteurization at 60ºC for ten hours[25]. Albumin concentration is used as a surrogate of liver function, and hypoalbuminaemia is a common feature in patients with cirrhosis. Recent research has shown that the function of albumin is impaired in patients with cirrhosis[11]. Albumin dysfunction may be due to either saturation with bilirubin and structural modifications. The difference between albumin and endogenous albumin should be taken into consideration, as well as between different albumin formulations. Albumin is hypo-osmolar compared to human plasma but with higher sodium and chloride concentrations. There may also be differences in oxidation and metal ions among different albumin products and storage conditions may lead to biochemical changes[13]. These may not be relevant for volume expansion but could modify albumin function. The main synthetic plasma expanders are crystalloid solutions (sodium chloride, Ringer) and non-protein colloids (dextran, polygeline, hydroxyethyl starch)[33]. Recombinant human albumin has shown pharmacokinetic equivalence in studies, it has only been licensed for using in pharmacological industry due to concerns about immunogenic host cell products[34] and also industrial manufacture of recombinant albumin is currently not cost-effective. However, the potential production of genetic isoforms of albumin provides beneficial characteristics, such as antibacterial properties or bilirubin affinity, which may boost the utility of recombinant albumin in the future. The affirmative function of albumin beyond volume expansion is a growing and promising field. Future clinical research should explore the unique property of albumin that modulate the biological functions and disease processes in liver disease, sepsis and in other diseases where albumin dysfunction might play a crucial role in their pathophysiological processes and would be of value in treating critical patients.

Conflict of interests:

None

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