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ALBUMINS IN SOLID TUMOR PATIENTS

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Summary

The manufacture of albumin derived from human plasma started by Professor E. J. Cohn during World War II has expanded into international business over the past sixty years (1). In vital situations, albumin was used as a plasma expander. This is a biological preparation and always potentially dangerous. The manufacture of albumin is getting more and more expensive as the preparation has to meet standards ever higher. With the market abundant in artificial macro-molecular plasma expanders, improved parenteral nutrition, and studies questioning the effectiveness of albumin use, the administration of albumin has been reduced. Because of the nature of their disease and chemoradiotherapy treatment, patients with tumors are prone to having low protein levels. However, indications for albumin therapy are restricted, the same as that in other patient groups. With the quality parenteral and enteral nutrition available, the use of albumin to correct hypoalbuminemia is not justified.

KEYWORDS: *hypoalbuminemia, albumin physiology, calculating albumin dosage, albumin administration*

ALBUMINI U BOLESNIKA SA SOLIDNIM TUMORIMA

Sažetak

Proizvodnju albumina iz ljudske plazme započeo je profesor Cohn E. J. tijekom Drugog svjetskog rata, koja je u posljednjih šezdesetak godina prerasla je u internacionalni biznis (1). U vitalnim situacijama, albumin je upotrebljavan kao plazmaekspander. To je biološki preparat i uvijek je potencijalno opasan. Proizvodnja albumina sve je skuplja, jer preparat mora zadovoljavati sve više i više standarde. Uz bogato tržište umjetnih makromolekularnih plazmaekspandera, unaprijeđene intravenske prehrane i studije koje govore o upitnom djelovanju albumina, njegova primjena je u padu. Tumorski bolesnici, zbog prirode bolesti i liječenja kemoradioterapijom, skloni su nižim razinama proteina. Međutim, indikacije albuminske terapije su restriktivne, iste kao i kod ostalih skupina bolesnika. Uporaba albumina za korekciju hipoalbuminemije nije opravdana pored kvalitetne parenteralne i enteralne prehrane.

KLJUČNE RIJEČI: *hipoalbuminemija, fiziologija albumina, računanje doze albumina, primjena albumina*

INTRODUCTION

Albumin is a transport protein in human plasma. Hypoalbuminemia develops because of albumin synthesis disorders caused by protein malnutrition and liver damage, protein loss in the nephrotic syndrome, enteropathy, burns and bleeding. Accelerated degradation due to inflammation, uneven distribution due to the slowed lymphatic flow or increased vascular permeability, and hemodilution also result in a decrease of albumin levels. Some people are born without and live without albumin (Table 1). Cachectic syndrome, reduced appetite or body weight loss can develop associated with tumor disease. The prevalence of cachexia ranges from 50 to 80% before death, and cachexia is the immediate cause of death in 20% of patients (2). Abnormalities in the

mouth and gastrointestinal tract may be caused by the disease or treatment. In cancer patients, loss of taste and smell frequently occurs following chemotherapy and radiation treatment. By treating cancer cachexia is treated, too. However, in advanced cases, food intake should be increased to avoid loss of muscle and fat. In the inflammatory state, the body produces more immunoglobulin and less albumin. The level of acute phase response proteins, pro-inflammatory cytokines is increased, and protein catabolism, lipolysis and anaerobic glycolysis are accelerated. The rates of both protein synthesis and lipogenesis are reduced. All of this leads to a decrease in body mass and cachexia. A similar situation occurs in tumor patients as a result of inflammation that develops around the tumor. Tumor necrosis factor α (TNFα) is elevated in cachectic patients. TNFα given to mice results in a decrease in albumin mRNA level and albumin synthesis (3). In tumor patients, similar mechanisms can lead to the lack of albumin in plasma.

Table 1.

COMMON CAUSES OF HYPOALBUMINEMIA

HYPOALBUMINEMIA < 20g/L	
SYNTHESIS	**DISTRIBUTION**
Protein malnutrition Liver damage	Slowed lymfatic function Increased vascular permeability
LOSS	**DILUTIONS**
Nephrotic syndrome Enteropathia Burns Bleeding	Compensatory therapy
DEGRADATION	**HERITAGE**
Inflammation	Analbuminemia < 1g/L

THE PHYSIOLOGY OF ALBUMIN

Albumin is a transport protein, with a molecular mass of 66.3 kDa, maintainer of colloid osmotic pressure, scavenger of free radicals and antioxidant (4). Albumin is synthesized in the liver, and is the only plasma protein that contains no carbohydrate. The albumin preparation, as obtained from many donor units of plasma, shows a high biological diversity and is a potential transmitter of any infection. As a carrier of oligomers, polymers, endotoxins, hema particles, precalicrein, bradykinin, it can cause anaphylaxis.

The rate of albumin synthesis and degradation is 0.2g/kg of body weight per day. This means that a dose in a 70 kg man is 14g per day. The rate of albumin synthesis can be accelerated 2-3 times by stimulation with thyroxin, insulin, glucocorticosteroid, anabolics and protein rich foods.

The total exchangeable albumin is 5g/kg of body weight. In a 70 kg man the total body albumin is 350 g, of which 60% is located in the intravascular space, and 35- 40% in the skin and muscles. In the liver, there is approximately only 0.3 g. Hepatocytes are responsible for the synthesis of albumin and its release into the hepatic venous circulation. Albumin in plasma may vary by 15%, depending on body position, i.e. sitting or standing. Daily, 0.1 g of albumin is lost into the gastrointestinal tract and 15 mg is excreted in the urine.

The half-life of albumin is approximately 2-3 weeks. The reference interval is 29-54 g/L or 50-67% of total plasma proteins ranging between 58-80 g/L. A fall in the albumin concentration to 20 g/L diminishes the colloid osmotic pressure from 24 mmHg to 12 mmHg, and fluid from the capillaries passes into the interstitium causing edema (5). A gram of albumin binds 18 mL of water per hour (6). A pregnant woman has 20% lower albumin levels due to increased extravascular fluid volume. Inflammation reduces albumin levels with its synthesis showing a compensatory reduction on account of acute-phase proteins. Chronic inflammation and gammopathies cause hypoalbuminemia. Hypoalbuminemia is commonly encountered in cirrhosis of the liver, and also in exicosis, i.e. in the dried out, dehydrated body.

ALBUMIN DOSE DETERMINATION

In Croatia, albumin preparations are available in two dosage forms: 250 mL 5% (12.5 g of albumin per dose) and 50 mL 20% (10 g of albumin per dose). To reach a particular albumin concentration in a patient the following equation is used:

Required albumin dose (g) = target albumin concentration (g/L) – actual albumin concentration (g/L) x plasma volume

Plasma occupies 0.035 L/kg body weight and in a 70 kg man is calculated as follows:

70kg x 0.035 L/kg = 2.45 L.

An example of calculating an albumin dose required in a 70 kg man:

Required albumin dose (g) = target concentration 40 g/L – actual concentration 20 g/L x plasma volume 2.5 L = 50 g.

If we want to raise the albumin concentration from 20g/L to 40g/L in a 70 kg man, 50 g of albumin will be administered i.v. (= 5 doses x 50 mL of 20% albumin or 4 doses x 250 mL of 5% albumin), (Figure 1).

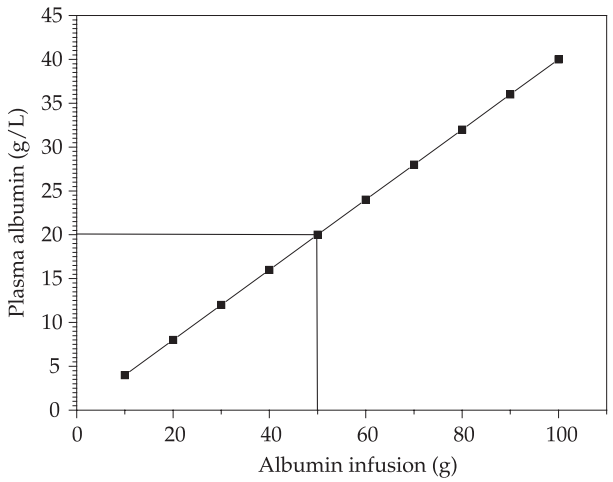

Figure 1. Graphical representation of increased plasma albumin concentration following albumin infusion.

It may be said that 10 g of albumin administered i.v. raises the plasma albumin level by 4 g/L. Albumin at concentration of 5% in a dose of 1L i.v. (contains 50 g of albumin, the same as in 1L of plasma) raises the plasma volume and plasma albumin concentration by 1L and 20g/L, respectively.

ALBUMIN ADMINISTRATION

Albumin used to maintain circulatory blood volume is administered only after an infusion of 2 L of crystalloid solutions or maximum allowable amount of colloid solutions did not produce hemodynamic stability. Albumin is also given in exceptional circumstances where there are contraindications to administration of non-protein infusion solutions, when salt intake should be limited, for hypovolemia with an albumin level <20 g/L, hemorrhagic shock, plasma loss, infection and toxicosis, acute liver failure, cirrhosis of the liver, burns, extensive cellulites, mediastinis, pancreatitis, peritonitis, nephrotic syndrome, hyperbilirubinemia, long-term starvation, cerebral edema and acute respiratory-distress syndrome (ARDS).

The albumin preparation does not potentate the furosemide natriuresis. In renal tubules, the preparation binds to furosemide, blocks it and reduces its diuretic effect. It raises both the volume and the flow of plasma through the kidney, but

Table 2.

ADMINISTRATION OF ALBUMIN INFUSIONS

ALBUMIN ADMINISTRATION		
INDICATIONS		CONTRAINDICATIONS
Hypoalbuminemia <20 g/L	Complication of enteral feeding (diarrhea) Crystalloid-resistant hypotensions	- Hypoalbuminemia (except for this referred to in the indications) - Hypovolemia (except for this referred to in the indications) - Undernutrition - Chronic nephrotic syndrome - Chronic liver failure - Peripheral edema
Ascites evacuation (paracentesis)	After 1 liter, per liter of ascites, 50 mL of albumin 20%	
Ascites evacuation (diuretics)	Albumin <25g/L, not responding to diuretics, administer albumin 20%, not above the limit of 30 g/L	
Subarachnoid hemorrhage	Only under conditions of: pure subarachnoid bleeding - 4-8 days following the bleeding - Euvolemia, hypovolemia, central venous pressure normal or high - Vasospasm occurrence (clinical transcranial doppler), hyponatremia, 250 mL of 5% albumin every 8-12 hours until central venous pressure maintenance is achieved. Reduce the dose when symptoms improve.	
Burns	Start after 24 hours in adults, after 12 hours in children, if burns cover >20% of the body area in adults, and >15% in children, elderly, for electrical and deep burns. The albumin level to be maintained at a minimum of 25 g/L	
Plasmopheresis	Volume replacement with 5% albumin	

diminishes glomerular filtration rate. A paradox! The reason remains unknown.

With albumin treatment immunoglobulin levels are reduced (reduced response to vaccines). Its negative charge binds to ATIII to neutralize the coagulation factor Xa, and similarly, produces anti-aggregation effect on blood platelets. Hypercoagulation in nephrotic syndrome can be explained by the lack of albumin.

During hypovolemic shock, albumin may be infused at a rate of 5-10 ml/min, and in patients with almost normal blood volume, at a rate of 2-4 mL/min. Human albumin administration requires regular monitoring of hemodynamic indicators: arterial blood pressure, heart rate, central venous pressure, pressure in the pulmonary artery, diuresis, electrolytes, hematocrit and hemoglobin. The total allowable dose of albumin is 250 g (5L 5% = 20 doses x 250 mL 5% or 1.25 L 20% = 25 doses x 50 mL 20% albumin through 48 hours).

Contraindications for albumin administration include: allergic reaction to albumin, hypertension, decompensated heart failure, circulation disorder, marked anemia, liver cirrhosis with portal hypertension, esophageal varices, hemorrhagic diathesis.

Albumin infusion is efficacious in hypovolemic shock and cardiopulmonary operation. Its efficacy in extensive cellulites, liver damage, mediastinitis, pancreatitis and prophylaxis of renal failure has also been shown. It is not efficacious in chronic cirrhosis of the liver and metabolic disorders.

RISKS OF ALBUMIN THERAPY

Albumin therapy can cause bradycardia/tachycardia, hypotension/hypertension, nausea, vomiting, fever, shivering, symptoms of circulation problems. Serious adverse events occur with an incidence of 1.29×10^6 albumin doses (7). Fatal serious adverse events are reported at an incidence of 5.24×10^8 albumin doses (8). Human plasma preparations are potential risk carriers (prions, unknown agents). The Cochrane review showing a 6% higher mortality rate in albumin-treated patients compared with those receiving other plasma expanders had an impact on a reduced albumin use (9). In response, plasma industry launched global promotion of albumin worth 1.4 million pounds (22 million $) (10). Following a new Cochrane review and several SAFE studies, it has been concluded that albumin neither raises nor reduces the mortality risk, and that there is no difference in mortality between albumin- and saline-treated groups (11-13).

CONCLUSION

A very restricted use of albumin is recommended. A theoretically useful pharmacological action does not justify albumin administration that is without any practical effect on the patient. On one hand, actual data show that it is recommended not to use albumin as a plasma expander when more efficacious synthetic preparations with fewer side effects are available. On the other hand, manufacturers' propaganda is pitiless. With the quality parenteral and enteral nutrition available, the use of albumin to correct hypoalbuminemia is not justified (14). Some of potential indications for albumin therapy would be liver transplantation and liver surgery, severe burns, and neonates. Controversial indications would include: liver diseases, ascites, paracentesis, malnutrition, long-term starvation, pancreatitis, peritonitis. People born without albumin live normally and have no greater problems due to their albumin lack (15). It has been shown that albumin therapy rationalization in a 7-bed intensive care unit results in savings of 7.000 $ a month (16).

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