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Review

The Therapeutic use of human albumin in cancer patients' management

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ABSTRACT

Human albumin (HA) has been widely used in clinical practice due to its unique physiological characteristics and pharmacokinetics. However, with the absence of clear institutional recommendations, its uncontrolled prescription remains largely controversial. An extensive review on the albumin chemistry, pharmacology, physiology and pathology was performed, and data on commercially available HA, its cost, medical usage and the related available guidelines, particularly in oncology patients were gathered.

Studies assessing the appropriate use and safety of HA in cancer patients are lacking. A retrospective survey of the appropriateness of HA infusions according to the SIMTI guidelines (2009) was performed in our department. Among 53 patients who received HA infusions, only 5.7% of the indications were appropriate for HA administration. Occasionally appropriate and inappropriate indications were considered in 10% and 84.3% of the prescriptions respectively with a relatively high cost. The adoption of strict guidelines may substantially reduce the inappropriate use and the subsequent healthcare costs.

1. Introduction

Human albumin (HA) has been widely used in the clinical setting based on its pathophysiology rather than evidence-based clinical trials, until concerns about its prescription started to emerge. Several clinical trials, often contradictory, have been carried out in recent years to define the appropriate use of this significantly costly product. Surprisingly, despite being frequently prescribed in cancer patients, large surveys targeting the use of this solution in this particular population are almost inexistent. For instance, in one study, prescriptions of HA in an Hematology and Oncology department in a hospital accounted for 17% of all prescriptions, coming fourth in frequency after the internal medicine, surgery and gastroenterology departments (Vargas et al., 1997).

In order to review the human albumin use in cancer patients, we performed an electronic search of MEDLINE from the PubMed database until 2016. We used the keyword: Albumin in combination with the following terms: use; infusion; prescription; administration; supplementation; abuse; appropriate; indications; recommendations; cancer; oncology; and hematology. Additional references were identified by searching the bibliographies of relevant articles. We only included papers in the English language. We first screened the retrieved articles starting from titles and abstracts then analyzed the entire texts to select the papers that most respond to our objectives; with emphasis on review articles.

2. Human albumin structure

HA is a polypeptide of 585 amino acids. It is a stable, highly soluble, and negatively charged molecule with a relatively small molecular weight (about 66 KDa) (Margarson and Soni, 1998; Quinlan et al., 2005). The protein contains three homologous domains each consisting of two subdomains A and B, composed of four and six α-helices respectively. Most of its thirty-five cysteine residues form disulfide bridges that contribute to its tertiary structure. A single free cysteine residue provides a reactive thiol group, which participates in reactions that are essential to the in-vivo function of the protein (Quinlan et al., 2005).

3. Pharmacokinetics

3.1. Synthesis and catabolism

In the physiological state, 9–12 g of HA are synthesized per day in the polysomes of hepatocytes. With a half-life of two to three weeks, the molecule is catabolized at the same rate in or adjacent to the tissue vascular endothelium. Hepatocytes lack the ability to store the HA, but can increase the synthesis rate two to three folds following a change in

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the colloid osmotic pressure or in the osmolality of the hepatic extravascular space. Other factors that influence HA synthesis are insulin, cortisol and thyroxine (Margarson and Soni, 1998; Farrugia, 2010; Pietrangelo et al., 1992; Kimball et al., 1995; Takagi and Ogata, 1968). Pre-albumin is another non-glycosylated protein synthetized and catabolized by the hepatocytes. It is not a precursor of albumin synthesis but was named so because it migrates earlier than albumin on electrophoresis. This protein is rich in the essential amino acids, especially tryptophan, and unlike albumin, has a short half-life of 1.9 days which makes it a greater marker for the assessment of acute changes in the nutritional status. However, in clinical practice, pre-albumin assessment is limited due to its high cost (Dellière and Cynober, 2016).

3.2. Distribution

HA is primarily an extravascular protein, accounting for 50% of the total plasma protein concentration (approximately 0.6 mmol/L or 40 g/L). The interstitial concentration is around 14 g/L, and varies from one region to another within the interstitium (Margarson and Soni, 1998; Quinlan et al., 2005).

3.3. Circulation

Physiologically, albumin leaves the intravascular space into the interstitium then returns via the lymphatic system, with a circulatory half-life of 16–18 h. A state of equilibrium is maintained between the different compartments, influenced by the *trans*-capillary escape rate (TER), which is equal to 4–5% in a healthy individual, and by the lymphatic flow on which depend the clearance of HA from the interstitium. Lymphatic flow is estimated to be at 120 mL/h in a healthy individual where proteins occupy approximately 80% of the plasma volume (Margarson and Soni, 1998; Doweiko and Nompleggi, 1991). Serum albumin levels in the healthy individual range from 35 to 45 g/L (Gatta et al., 2012).

4. Physiological properties of HA

The unique structural properties of HA provide it with many physiological functions including maintenance of the colloid osmotic pressure (Margarson and Soni, 1998), ligand binding and drugs transport (Margarson and Soni, 1998; Kragh-Hansen, 1990), free radical scavenging ((Halliwell, 1988)) anti-oxidant function (Evans, 2002), role in the process of platelet aggregation (Simon et al., 1993; Doweiko and Bistrian, 1994), effect on vascular permeability (Ramirez-Vick and Vargas, 1993) and participation in intracellular signaling pathways (Cantin et al., 2000). However, few evidence on the significance of each of these properties exists, thus not all of them are correlated to its use in clinical practice.

5. Serum albumin modification in disease states

5.1. Causes of hypoalbuminemia

Hypoalbuminemia is defined by albumin serum levels lower than 35 g/L. However, it usually becomes clinically significant for levels < 25 g/L (Gatta et al., 2012). Low serum albumin levels are observed in elderly patients, especially in hospitalized patients, and in states of malnutrition and chronic illness. Mechanisms of hypoalbuminemia include decrease in amino acids or energy supply, impaired liver synthesis, increased loss (renal or gastro-intestinal), increased tissue catabolism or distributional issues (Franch-Arcas, 2001).

5.2. Hypoalbuminemia in cancer

Recent studies have shown that albumin undergoes a biphasic response to stress in disease states like cancer: an initial decrease in albumin synthesis mediated by pro-inflammatory cytokine secretion, followed by an overall increase (Margarson and Soni, 1998; Castell et al., 1990). Other mechanisms of hypoalbuminemia in cancer patients have been proposed, most importantly the increased catabolism and cachexia (Gatta et al., 2012; Małkowski, 2013). Moreover, increased vascular permeability, manifesting by an increased TER in these patients contributes to the redistribution of albumin from the intravascular sector towards the interstitium, thus leading to a decreased serum albumin level (Fleck et al., 1985). Comorbid states frequently associated with cancer, such as chronic liver or renal disease, sepsis and gastrointestinal bleeding also contribute to hypoalbuminemia by various mechanisms (Małkowski, 2013).

Cachexia in cancer results from multiple factors including cytokine-induced anorexia, anatomic inability for nutrients intake, hypercatabolism and metabolism changes, and treatment-related side effects (nausea, vomiting, diarrhea, mucositis and others). Serum albumin is known to be an important biological factor used in the assessment of nutritional status, especially in elderly patients. Frail, malnourished elderly have a defective immune system predisposing them to more opportunistic infections. Serum albumin levels lower than 35 g/L together with impaired nutritional status in elderly patients with cancer is predictive of poor outcome and greater mortality (Blanc-Bisson et al., 2008) In fact, many studies confirmed that low serum albumin levels are predictive of morbidity and mortality with poor prognosis in both solid and hematological tumors (Stuart et al., 1996; Kemeny et al., 1989; Steinberg et al., 1992; Parker et al., 1994; Warwick et al., 1995; Johnson et al., 1993; Lee, 1985; Falconer et al., 1995; Sirott et al., 1993; Levis et al., 1991; Bladé et al., 1989; Komrokji et al., 2012).

5.3. Hyperalbuminemia

Hyperalbuminemia is not commonly addressed in the literature due to the rarity of this condition. It has been reported in patients with anorexia nervosa or in cases of high-protein diet (Thibault and Roberge, 1987; Mutlu et al., 2006). Nonetheless, the pathophysiology of Hyperalbuminemia has not been well elucidated.

6. Commercially available albumin

The first stable albumin solution was developed by Edwin Cohn during the World War II. New methods of fractionation, purification and separation were later introduced to obtain products of variable stability, efficiency and safety (Farrugia, 2010). The process of HA sterilization by ultrafiltration prevents any disease transmission despite being derived from pooled human plasma. HA solutions are commercially available as 4.5%, 20% and 25% solutions, the latter being hyperoncotic mainly used for plasma volume expansion. All preparations contain 130–160 mEq of sodium per liter, approximately 96% albumin, while the rest contains globulins (Chakravorty et al., 2004).

7. Human albumin use in clinical practice

HA has long been prescribed for volume replacement especially in critically ill patients. This is probably the most controversial indication. Data emerging from several randomized controlled clinical trials clearly argued against its use in this setting with the absence of clear benefit in reducing mortality (Wilkes and Navickis, 2001; Finfer et al., 2004; Cochrane Injuries Group Albumin Reviewers, 1998). In fact, in the latest update in 2013, the Cochrane reviewers again found that there is no evidence that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids (Perel et al., 2013). While these disparities may be due to addressing mortality as the primary endpoint, several reports compared the use of albumin versus different crystalloids for volume expansion in terms of morbidity, and suggested that HA could be beneficial and safe in diverse clinical settings (Haynes et al., 2003; Vincent et al., 2005). Unfortunately, similar data in