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Position Paper

AISF-SIMTI Position Paper: The appropriate use of albumin in patients with liver cirrhosis

Italian Association for the Study of the Liver (AISF)
Italian Society of Transfusion Medicine and Immunohaematology (SIMTI)

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ABSTRACT

The use of human albumin is common in hepatology since international scientific societies support its administration to treat or prevent severe complications of cirrhosis, such as the prevention of post-paracentesis circulatory dysfunction after large-volume paracentesis and renal failure induced by spontaneous bacterial peritonitis, and the treatment of hepatorenal syndrome in association with vasoconstrictors. However, these indications are often disregarded, mainly because the high cost of human albumin leads health authorities and hospital administrations to restrict its use. On the other hand, physicians often prescribe human albumin in patients with advanced cirrhosis for indications that are not supported by solid scientific evidence and/or are still under investigation in clinical trials.

In order to implement appropriate prescription of human albumin and to avoid its futile use, the Italian Association for the Study of the Liver (AISF) and the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) nominated a panel of experts, who reviewed the available clinical literature and produced practical clinical recommendations for the use of human albumin in patients with cirrhosis.

1. Introduction

The clinical use of human albumin (HA) dates back to World War II when it was administered for fluid resuscitation. Since then, its administration has been extended to many other diseases since physicians commonly believe in its efficacy. However, apart from some clinical indications for which its use is supported by solid scientific evidence, in many other settings the efficacy of HA has been disproven by evidence-based medicine or is still under debate.

Hepatology is an area in which the use of HA is particularly common, since this treatment is currently employed to treat or prevent severe complications of cirrhosis. Randomised clinical trials and meta-analyses have demonstrated its efficacy in the prevention of post-paracentesis circulatory dysfunction (PPCD) after large-volume paracentesis and renal failure induced by spontaneous bacterial peritonitis (SBP), and in the treatment of hepatorenal syndrome (HRS) in association with vasoconstrictors. Although endorsed by international scientific societies [1,2], these indications are often disregarded, even in specialised centres, mainly because the high cost of HA leads health authorities and hospital administrations to restrict its use. On the other hand, physicians often prescribe HA in patients with advanced cirrhosis for indications that are not supported by solid scientific evidence and/or are still under investigation in clinical trials. This inappropriate use may limit the availability for the patients in whom HA administration is supported by solid scientific evidence.

In order to implement appropriate prescription of HA and to avoid its futile use, the Italian Association for the Study of the Liver (AISF) and the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) nominated a panel of experts, who reviewed the available clinical literature and produced practical clinical recommendations for the use of HA in patients with liver cirrhosis. The initial draft was revised by a second panel of experts identified by the two scientific societies, so that the final version resulted from the consensus of the two working groups.

The level of evidence and strength of recommendation were judged according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system [3]. The strength of the evidence has been classified into four levels: high (A), moderate

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Table 1
Grading evidence and recommendations (adapted from the GRADE system).

Quality of evidence	
A – High	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multicentre trial
B – Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C – Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D – Very low	Any estimate of effect is very uncertain. Expert opinion • No direct research evidence • One or more studies with very severe limitations
Strength of recommendation	
1 – Strong	Factors influencing the strength of the recommendation included the quality of evidence, presumed patient-important outcomes, and cost.
2 – Weak	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty: high cost or resource consumption

(B), low (C), and very low (D) quality, while that of the recommendation has been divided into two: strong (1) and weak (2) (Table 1). Where no clear evidence exists, the recommendations are based on the consensus advice of the writing committee and the expert opinion(s) reported in the literature.

2. The albumin molecule

2.1. Structure

HA is the main circulating protein in healthy individuals (3.5–5 g/dL), accounting for about 50% of the plasma proteins. It is a small protein (molecular weight: 66.5 kDa), consisting of a single chain of 585 amino acids organised in three repeated homologues domains (I, II, and III), each of which comprises two separate subdomains (A and B). Of the 35 cysteine residues of the molecule, 34 are involved in internal disulphide bonds which stabilise the spatial conformation of the molecule, while the cysteine at position 34 (Cys-34) remains free in the reduced form, thus representing the major functional site of HA [4].

2.2. Metabolism

HA is synthesised by hepatocytes and released into the circulation (about 10–15 grams every day). Its synthesis is stimulated by hormonal factors, such as insulin, cortisol and growth hormone, while pro-inflammatory mediators exert an inhibitory effect. Once produced, approximately 30–40% circulates in the blood stream, while the remaining leaves the vascular compartment at a rate of 5% per hour (transcapillary escape rate) and returns to it via the lymphatic system; the amount that returns to the vascular compartment is the same as the amount that leaves it. The circulatory half-life of HA is approximately 16–18 hours, while its total half-life varies from about 12 to 19 days in healthy young adults. HA is mainly degraded by the muscles, liver and kidneys, although many other tissues can participate in its catabolism [4–6].

2.3. Properties

HA is the main modulator of fluid distribution in the various compartments of the body accounting for about 70–80% of the plasma oncotic pressure. Two-thirds of the oncotic capacity derives from the direct osmotic effect related to its molecular mass and high plasma concentration while one-third is the results of the Gibbs-Donnan effect, due to the negative net charge of the molecule that is consequently able to attract positively charged molecules (i.e. sodium and, therefore, water) into the bloodstream [4–6].

HA has many other biological properties that are unrelated to the regulation of fluid compartmentalisation (Fig. 1). Some of these non-oncotic properties assume particular importance, such as scavenging and detoxification of reactive oxygen and nitrogen species, binding and transport of many hydrophobic endogenous molecules (e.g., cholesterol, fatty acids, bilirubin, thyroxine) and exogenous ones (e.g., drugs, including many antibiotics), preservation of the functional integrity of the microcirculation (e.g., endothelial stabilisation and platelet anti-aggregation), and modulation of the immune and inflammatory responses (e.g., binding of endotoxins, prostaglandins, and pro-inflammatory cytokines) [4,5].

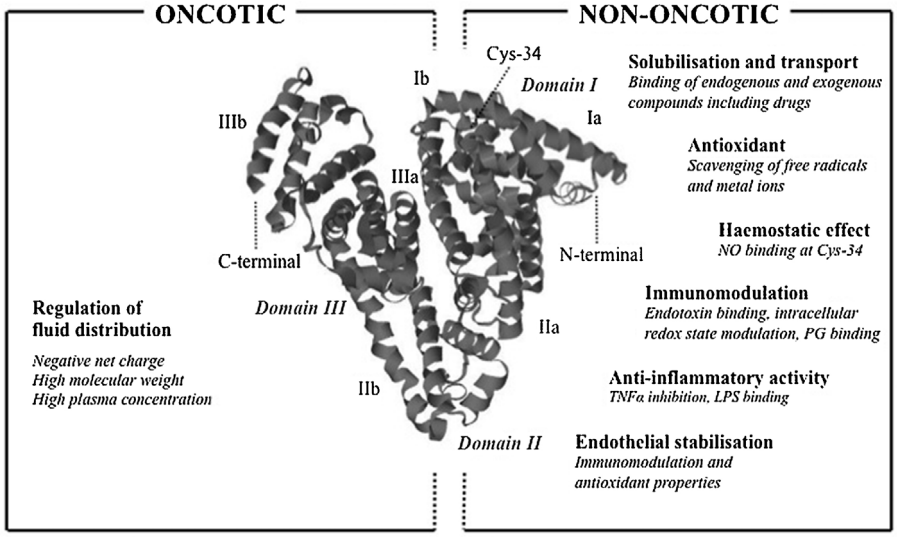

Fig. 1. Oncotic and non-oncotic properties of human albumin. Cys-34, cysteine-34; LPS, lipopolysaccharides; NO, nitric oxide; PG, prostaglandins; TNFα, tumour necrosis factor-alpha.