Leading article

Is there still a need for albumin infusions to treat patients with liver disease?

The course of patients with cirrhosis is frequently complicated by derangement of body fluid homeostasis which results in accumulation of large amounts of extracellular fluid in the peritoneal cavity and interstitial tissue.[1] Investigations performed in the 1940s proposed that the formation of ascites and oedema was related to an imbalance in Starling's equilibrium in splanchnic and systemic capillaries caused by increased hydrostatic pressure due to portal hypertension and reduced oncotic pressure because of the low serum albumin levels characteristic of cirrhosis, which would favour the passage of fluid from the intravascular compartment to the interstitial tissue.[2–4] Later studies showed that patients with cirrhosis and ascites have marked circulatory dysfunction, characterised mainly by low systemic vascular resistance and arterial pressure, abnormal distribution of blood volume, with reduced central blood volume, and marked stimulation of vasoconstrictor and antinatriuretic systems (that is, the renin-angiotensin-aldosterone system and sympathetic nervous system).[5 6] In some patients this circulatory dysfunction is so intense that renal perfusion is greatly reduced leading to severe impairment of renal function, a condition known as hepatorenal syndrome.[7] Considering all of these factors it is not surprising that albumin infusions have been used for many years in the management of patients with cirrhosis and ascites in an attempt to reduce the formation of ascites and/or improve circulatory and renal function.[8] In the current decade the use of albumin in cirrhosis has regained attention because of the demonstration that patients with large ascites can be treated safely with large volume paracentesis associated with albumin infusions.[9] While some of these indications for albumin infusions are supported by the results of randomised studies, others are based on clinical experience and have not been proved in prospective investigations. Therefore, the use of albumin infusions in patients with cirrhosis is controversial. Recently, this debate has been fostered by the high cost and limited availability of albumin and the results of a meta-analysis showing that albumin administration may increase mortality in critically ill patients.[10]

This article will review the use of albumin infusions in the management of patients with cirrhosis and ascites on the basis of the current knowledge of the pathogenesis of ascites and renal dysfunction in cirrhosis. The information given does not apply to the clinical situation of patients with cirrhosis and dehydration because of excessive loss of extracellular fluid (that is, intense vomiting, diarrhoea, or overdiuresis) or gastrointestinal haemorrhage who should be treated with intravenous fluids or plasma expanders as in patients without liver disease under similar clinical conditions.

Pathogenesis of ascites and renal dysfunction in cirrhosis: role of circulatory dysfunction

Apart from sodium retention, the key factor for the development of ascites, patients with cirrhosis may also show impaired ability to eliminate water which may lead to dilutional hyponatraemia and renal vasoconstriction that, if severe, may result in hepatorenal syndrome.[1 7] Investigations carried out over the past two decades have provided convincing evidence indicating that these abnormalities of renal function and the formation of ascites in cirrhosis are related to a marked disturbance in circulatory function.[11–13] This circulatory dysfunction consists of reduced total systemic vascular resistance, arterial hypotension, and high cardiac output. Total blood volume is not reduced, as proposed initially by the classical underfilling theory of ascites formation, but increased compared with that of healthy subjects. The reduction in total systemic vascular resistance is mainly due to marked arterial vasodilatation in the splanchnic circulation because the resistance to blood flow in non-splanchnic vascular beds (that is, upper and lower limbs, kidneys, and brain) is normal or even increased.[11–13] The exact mechanism(s) leading to this vasodilatation is not completely understood but may involve increased synthesis/activity of vasodilator factors, including nitric oxide and vasodilator peptides.[14 15] The marked splanchnic arterial vasodilatation would be responsible not only for the reduction in total systemic vascular resistance but also for an abnormal distribution of blood volume with reduction of effective arterial blood volume (that is, the blood volume in the heart, lungs, and central arterial tree that is sensed by arterial receptors) and subsequent baroreceptor mediated activation of vasoconstrictor and antinatriuretic factors.[13] It is currently believed that this reduction in effective arterial blood volume is fundamental to the development of sodium retention in cirrhosis. The predominant accumulation of the retained fluid in the peritoneal cavity as ascites would be a consequence of a high filtration rate in the splanchnic capillaries resulting from both a backward and forward increase in hydrostatic pressure due to portal hypertension and splanchnic arterial vasodilatation, respectively, and an increased capillary filtration coefficient.[16 17] Dilutional hyponatraemia and hepatorenal syndrome are also pathogenetically related to circulatory dysfunction and depend, among other factors, on non-osmotic hypersecretion of antidiuretic hormone and the action of vasoconstrictor factors on the renal circulation, respectively.[1] Renal dysfunction in cirrhosis is of great clinical importance because its intensity correlates with prognosis.[1]

Effects of albumin infusions in the management of renal dysfunction in patients with cirrhosis and ascites

Albumin infusions have been used in the management of patients with cirrhosis and ascites with two main objectives: (1) to reduce the formation of ascites and oedema by increasing microvascular oncotic pressure; and (2) to improve circulatory and renal function by expanding total blood volume.[8] The first of these two effects was investigated in studies carried out between the 1940s and 1960s. Most showed that despite a pronounced increase in serum albumin levels and normalisation of oncotic

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pressure, the rate of ascites formation did not decrease consistently, even when albumin was given for prolonged periods.[18–21] Apart from proving the lack of efficacy of albumin for this purpose, the results of these studies were of pathophysiological relevance because they demonstrated that the decrease in oncotic pressure plays no significant role in the pathogenesis of ascites formation in cirrhosis.

Administration of plasma expanders has been used extensively in clinical practice to improve renal function in patients with cirrhosis and ascites despite the lack of available evidence supporting such an indication. Albumin has been the plasma expander most commonly used because of its greater oncotic potency and longer plasma half life compared with artificial plasma expanders.[22] Administration of albumin to patients with cirrhosis and ascites causes an increase in total blood volume followed by a moderate reduction, but not normalisation, of the activity of vasoconstrictor and antinatriuretic systems. These circulatory changes are associated with favourable effects on renal function, especially on renal plasma flow and glomerular filtration rate. However, these renal effects are modest and limited only to patients with normal or slightly impaired renal function, whereas patients with severe renal dysfunction do not show any beneficial response.[20 23–25] Suppression of the activity of antinatriuretic systems, particularly the renin-angiotensin-aldosterone system, probably accounts for an increase in the natriuretic response to diuretics observed in patients treated with repeated albumin infusions.[26] However, this beneficial effect is of small clinical relevance to justify the use of such therapy in patients with cirrhosis and ascites.

The reason why albumin infusions fail to consistently improve circulatory and renal function in patients with cirrhosis and ascites is not completely known. It may be related to the short lived effect of albumin in expanding total plasma volume because the transvascular escape rate of albumin (that is, the rate of albumin that escapes from the intravascular compartment to the interstitial tissue) is increased in patients with cirrhosis compared with that of healthy subjects.[27] However, this explanation seems unlikely because neither circulatory function nor renal function improve after repeated albumin infusions.[23] The most likely explanation is that albumin cannot increase effective arterial blood volume efficiently despite the increase in total blood volume because of the extreme vasodilatation present in the splanchnic circulation. The results of a recent study showing that in patients with advanced cirrhosis acute volume expansion is associated with a marked increase in non-central blood volume but no significant changes in central blood volume is in keeping with such a suggestion.[28] Moreover, this explanation is also supported by the observation that both circulatory and renal function improve markedly after the combined administration of albumin and ornipressin, a derivative of arginine vasopressin (the antidiuretic hormone) with marked vasoconstrictor activity in the splanchnic circulation.[29]

Effects of albumin infusions in the prevention of renal dysfunction in patients with cirrhosis and ascites

The circulatory dysfunction causing impairment in effective arterial blood volume and subsequent renal dysfunction in cirrhosis with ascites is not a fixed, unalterable disorder. Rather its intensity may increase as a consequence of the evolution of the disease or by intercurrent processes.

To date, two different situations that may further impair circulatory function in cirrhotic patients with ascites have been identified: large volume paracentesis and spontaneous bacterial peritonitis. Removal of large amounts of ascitic fluid is characterised by early favourable haemodynamic effects with suppression of vasoconstrictor and antinatriuretic factors and increased plasma natriuretic peptide levels. However, this is followed by a second phase characterised by marked activation of vasoconstrictor and antinatriuretic factors in the absence of changes in plasma volume, consistent with impairment of effective arterial blood volume.[9] This post-paracentesis circulatory dysfunction occurs in most patients treated with large taps, is not spontaneously reversible, and is associated with impairment of renal function and decreased survival.[9 30 31] The occurrence of such circulatory dysfunction and the subsequent development of dilutional hyponatraemia and renal failure after large volume paracentesis can be prevented successfully by administration of albumin (8 g/l of ascites removed).[9 30 31]

A second condition that may impair circulatory function in patients with cirrhosis and ascites is spontaneous bacterial peritonitis, a disorder characterised by spontaneous infection of ascites due in most cases to the passage of bacteria from the intestinal flora to the ascitic fluid.[32] Patients with spontaneous bacterial peritonitis frequently develop changes in circulatory function consistent with impairment of effective arterial blood volume, which is associated with renal failure in approximately one-third of patients. This impairment in renal function is probably related to the high level of cytokines and vasodilator factors in plasma and ascitic fluid, occurs despite the resolution of the infection by antibiotic therapy, and is associated with an impaired prognosis.[33 34] The efficacy of albumin in the prevention of circulatory and renal dysfunction in patients with cirrhosis and spontaneous bacterial peritonitis has been assessed recently in a prospective, randomised study in which patients received either conventional antibiotic therapy alone or in association with albumin infusions (1.5 g/kg body weight at the time of diagnosis of the infection and 1 g/kg two days later).[35] The results of this study showed that the occurrence of circulatory dysfunction, as assessed by changes in the activity of the renin-angiotensin-aldosterone system, and renal failure were much lower in patients treated with albumin infusions than in those who received antibiotic therapy alone, despite a similar rate of infection resolution. Most importantly, administration of albumin infusions was associated with a longer survival. These results, therefore, support the use of albumin infusions as a regular treatment for spontaneous bacterial peritonitis in patients with cirrhosis.

Role of albumin infusions in the treatment of hepatorenal syndrome

Hepatorenal syndrome represents the extreme expression of circulatory dysfunction in cirrhosis with ascites.[1 7 12 13] This condition is characterised by very low arterial pressure and total systemic vascular resistance, marked overactivity of vasoconstrictor factors (renin-angiotensin and sympathetic nervous systems, antidiuretic hormone, and endothelin), and marked arterial vasoconstriction in the kidney and other vascular territories (muscle, skin, and brain). Plasma volume expansion with albumin, as well as other procedures that cause expansion of total blood volume (infusion of ascitic fluid or peritoneovenous shunting), have traditionally been used in the management of patients with hepatorenal syndrome with little success.[1 36] Although these therapeutic manoeuvres result in transient suppression of renal vasoconstrictor factors, which indicates amelioration of circulatory function, the increase in renal perfusion and glomerular filtration rate is only marginal. Similar findings have been reported with the use of vasoconstrictor drugs (ornipressin or midodrine).[1 36–38] However, two recent studies have shown that when cirrhotic patients with ascites and hepatorenal syndrome

are treated for several days or weeks with a combination of vasoconstrictors and plasma volume expansion with albumin infusions, a marked improvement in circulatory and renal function occurs in most cases with normalisation of plasma levels of vasoconstrictor factors and serum creatinine.[29 39] Interestingly, hepatorenal syndrome may not recur after treatment withdrawal and the survival of patients may be prolonged sufficiently in some cases to reach liver transplantation.

Summary and conclusions

There is a strong body of evidence indicating that renal functional abnormalities and ascites formation in cirrhosis are the final consequence of circulatory dysfunction characterised by marked splanchnic arterial vasodilatation causing a reduction in effective arterial blood volume and homeostatic activation of vasoconstrictor and antinatriuretic mechanisms. In contrast, there is no evidence to support a role for reduced vascular oncotic pressure due to hypoalbuminaemia in the pathogenesis of ascites.

Although albumin infusions have been used extensively in clinical practice in patients with cirrhosis to improve renal function and facilitate elimination of ascites, the beneficial effects of albumin are very modest and limited only to patients with slightly impaired renal function who respond to conventional therapy. Therefore, the available clinical evidence does not support the use of albumin infusions for such indications. In contrast, albumin infusions are very effective in preventing the deterioration in renal function associated with large volume paracentesis or spontaneous bacterial peritonitis, conditions that are known to cause impairment of circulatory function in patients with cirrhosis and ascites. Moreover, albumin infusions improve survival in patients with spontaneous bacterial peritonitis. Taken together, these data suggest that albumin can prevent renal impairment by maintaining effective arterial blood volume in situations characterised by acute deterioration in circulatory function. In contrast, when circulatory dysfunction is already established, albumin alone is not effective in improving renal function. The recent demonstration that concomitant administration of albumin and vasoconstrictor drugs acting preferentially in the splanchnic circulation normalises almost completely circulatory function and improves renal function in patients with cirrhosis and hepatorenal syndrome opens a new indication for albumin infusions in patients with liver disease.

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