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Icodextrin as first treatment: reasons to be optimistic

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Over the past 15 years, peritoneal dialysis has undergone considerable development from a technological point of view.[1,2] It is currently a fully validated form of dialysis treatment which is cheaper than haemodialysis and comparable in terms of survival rates and the effect on quality of life.[3-6] Nevertheless, haemodialysis continues to be the more commonly used replacement therapy all over the world. In 2001 data pertaining to 1,479,000 renal patients undergoing replacement therapies in 120 countries across 5 continents was published; peritoneal dialysis was only being used by 8.5% of patients while 69% of patients were being treated with haemodialysis.[7] The situation in Spain is similar.[8] There are several reasons behind this, some of which may seem illogical to some. The technique had a disastrous start when it was first introduced (with a high rate of peritonitis and obsolete technology) and this still casts a shadow over its reputation. Another factor is functional exhaustion of the peritoneum which some patients experience over the long-term and at least has some theoretical basis. The deterioration of the peritoneal membrane has been associated with the use of glucose as an osmotic agent. Its well-known deleterious effects on the peritoneum may lead to failure of the peritoneal dialysis treatment in the mid- to long-term.[9] With this in mind, an extensive effort has been made to find dialysis solutions that are more biocompatible, one of these being icodextrin.

Icodextrin is a cornstarch-derived glucose polymer and acts as a colloid osmotic agent. Its high molecular weight (16,000 Daltons) makes reabsorption difficult and therefore its ultrafiltration rate is steady for a longer period of time compared with glucose solutions.[10,11] Icodextrin ultrafiltration occurs across the small pores in the peritoneal membrane and is characterised by minimal lymphatic reabsorption. Ultrafiltration with a 7.5% icodextrin solution exchange is similar to that of a 3.86% glucose solution at 8 hours and is higher in dwell times of 12 hours.[12,13] It has been observed that in patients undergoing continuous ambulatory peritoneal dialysis the use of icodextrin during the overnight 8-12 hour dwell resulted in 500ml ultrafiltration, as compared with 300ml during the 14-16 hour long daytime dwell using the automated cycling technique. Neri et al.[14] have suggested that this may be due to the increase in lymphatic absorption caused by greater intraperitoneal pressure whilst standing up. Icodextrin solutions have a similar osmolarity to plasma (282mOsm/kg) and fewer glucose degradation products, which at least in theory makes them more biocompatible. The use of icodextrin is linked to improved volaemia in prospective studies.[15] It maintains residual renal function for longer and achieves better convective solute clearance.[16] In short, icodextrin represents a significant contribution in the management of patients that lose ultrafiltration. This will benefit high or fast transporters, moderate-high transporters[17,18] and possibly diabetics.[19] The increase in ultrafiltration is maintained over time and during episodes of peritonitis.

The peritoneum is a dialyzing membrane and as such undergoes functional and structural changes in the long-term that lead to the progressive deterioration of peritoneal transport.[20,21] Peritoneal fibrosis with progressive mesothelial thickening, neoangiogenesis and vasculopathy are some of the changes that can be attributed to the repeated exposure of the peritoneum to solutions that are not physiological or biocompatible, among other causes. These structural changes finally result in the functional failure of the peritoneal membrane for a variable percentage of patients.

Peritoneal membrane transport rates can be categorised as low, medium-low, medium-high and high, in accordance

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with the peritoneal equilibration test devised by Twardowski.[22] The higher the peritoneal transport rate, the lower the ultrafiltration rate and the higher the risk of volume overload. A high peritoneal transport rate is also associated with greater protein losses into the dialysate. The dialysate/plasma ratio of solutes with low molecular weight depends on the peritoneal vascular surface area. The increase in peritoneal vascularisation results in fast transporter status. This has been linked to an increase in mortality of up to 15%, especially in patients undergoing continuous ambulatory peritoneal dialysis and using glucose solution exclusively.[23-26] Other authors have not found any link between the peritoneal transport rate and patient mortality in the long term.[27] This apparent contradiction has prompted many authors to carry out in-depth studies on peritoneal transport rates at different stages during dialysis, in order to determine the influence of transport status on patient progress.

To investigate this, patients were divided into high transporter at the initiation of dialysis and those who acquired high transport status during follow-up.[28-30]

The incidence of fast transporters at the start of dialysis treatment (inherent high transporters) was 15%.[28,29] Similarly, a distinction was made between the two subtypes of high transport from the outset: type 1 is associated with comorbidity and inflammation and is accompanied by high IL-6 and VEGF plasma levels. This condition is associated with males, diabetics, low initial levels of albumin and increased baseline comorbidity. The prognosis for these patients is poor even if they are treated with haemodialysis. Type 2 is associated with high levels of CA125 in the peritoneal effluent, suggesting a large peritoneal surface area and, consequently, a large number of mesothelial cells. Type 2 has good prognosis if the peritoneum is unaffected by complications such as peritonitis and the patient remains euvolaemic, given that fast transport tends to normalise with time.[31,32]

Acquired high transport (type 3) may be transitory and reversible (for example during peritonitis) or permanent. The latter is developed by 30% of patients who have been undergoing peritoneal dialysis for a period of over 4 years. This is due to peritoneal neoangiogenesis caused by the exposure of the peritoneum to solutions that are not physiological (glucose, glucose degradation products, pH and lactate buffer) and peritoneal damage caused by complications like peritonitis. This is linked to an increased risk of overhydration, especially taking into consideration the loss of residual renal function after several years of peritoneal dialysis.

The treatment of high transporter status begins with its prevention. Some of the proposed measures include preserving residual function, preventing peritonitis and using icodextrin solution exchange during long dwell times and a cycler with short cycles to prevent hypervolaemia.[29] The use of ACE inhibitors may also be beneficial in the preservation of residual renal function during the first year of dialysis.[33]

In this issue, Fernández-Reyes et al.[34] analyse peritoneal transport in the short-term to mid-term in patients that have been using icodextrin from the outset. Their results showed that patients that used an icodextrin solution exchange tended to normalise peritoneal permeability. This finding was particularly evident in patients with high transport from the outset, and normalisation was greater when compared with that of patients who used glucose solution (control group). The study is particularly interesting since it included incident patients and the results are similar to those recently published in a prevalent population.[35] In this EAPOS sub-study, it was evident that the patients treated with icodextrin maintained adequate peritoneal function for at least two years, whereas those who received glucose solution experienced a significant deterioration in solute transport and ultrafiltration capacity with subsequent fluid overload. In the study by Fernández-Reyes et al.[34] the group of patients using icodextrin had suffered less episodes of peritonitis and a higher proportion of them were on ACE inhibitors at the start of the study. There is a need to carry out a randomized control study before any improvement in peritoneal transport can be attributed to icodextrin alone.

The way in which icodextrin improves peritoneal permeability in high transporters and the long-term benefits of icodextrin will be the subject of future studies.

KEY CONCEPTS

1. **Peritoneal transport status is a dynamic concept that varies over time and is influenced by different factors.**
2. **"High transporters" according to the classification system devised by Twardowski are also known as "fast transporters."**
3. **There are three types of fast transporters: inherent (type 1 and type 2) occurring at the initiation of treatment, and acquired (type 3).**
4. **The worst prognosis for fast transporters has been associated with the use of glucose solutions and manual technique.**
5. **Fast transporters should undergo automated peritoneal dialysis using icodextrin.**

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