Are High Flux Dialysers better for me than low Flux ones?

High-flux or low-flux dialysis: a position statement (edited for patients and caregivers) following publication of the Membrane Permeability Outcome study.

Introduction

The term 'flux' refers to the permeability of the membrane in the dialyser (artificial kidney) across which accumulated toxins and excess fluid pass during haemodialysis. In the past, this membrane was made from natural cellulose which has relatively small pores. The 'low-flux' cellulosic dialysers could easily remove the smaller toxins such as urea and creatinine, but larger molecules that are normally removed by normal kidneys were unable to fit through the pores. Modern dialyser membranes are made from synthetic polymers or chemically modified cellulose. The manufacturers of dialysers with synthetic membranes can engineer the size of the pores to be the same size as a cellulosic dialyser or much larger.

A 'high-flux' dialyser has a membrane that allows middle-sized molecules to pass through but prevents the accidental removal of protein from the blood. One example of a 'middle-molecule' is beta 2 microglobulin (B2M) which can cause amyloidosis (see explanation at the end of this appendix). If plasma is filtered through a high-flux membrane at least 70% of the B2M will pass through with the plasma water (in the specifications this will appear as a 'sieving coefficient of 0.7).

The more permeable membrane of a high flux dialyser also allows much faster removal of fluid. In haemodiafiltration, rapid removal (and replacement) of fluid is essential so high-flux dialysers are always used for this type of treatment. There are concerns that the easier passage of water through a high-flux could also make it easier for water borne contaminants, particularly endotoxins, to pass from the dialysis fluid back into the blood. Endotoxins are fragments of bacteria that can be small enough to pass through the dialyser membrane. If endotoxin gets into the blood, either through the dialyser membrane or though damage to the lining of the intestines, it can provoke an inflammatory response from the body's immune system. Fortunately most synthetic membranes adsorb (trap) endotoxin which keeps it from entering the blood stream. But to minimise the risk of exposure, the machine can be fitted with an extra filter through which the dialysis fluid is passed to ensure that it is 'ultrapure'.

The current guidelines for adequacy of dialysis are all based on the removal of urea and the recommended dose (in units of 'Kt/V') can be achieved with both low and high flux dialysers. Failure to achieve the minimum Kt/V, especially in patients who have no residual kidney function, has an impact on well-being and survival relatively quickly. The problems associated with inadequate removal of the larger toxins tend to be long term which makes it much harder to study the benefit of more efficient removal.

Current guideline

A summary of the current European guideline relating to dialyser membrane permeability or

flux is contained in the EBPG guideline on dialysis strategies, published in 2007 and states:

Guideline 2.1: The use of synthetic high-flux membranes should be considered in order to delay long-term complications of haemodialysis therapy. Specific indications include: reduction of dialysis-related amyloidosis (See explanation at the end of this appendix); improving control of hyperphosphataemia (See explanation at the end of this appendix); reducing cardiovascular risk; and improving the control of anaemia.

When this guideline was published, there was insufficient evidence to link membrane permeability with survival. The guideline cited the haemodialysis study (HEMO) as the only randomized clinical trial (RCT) then available that directly addressed the influence of high-flux dialysis on survival. Although this study found no difference in survival between high- and low-flux dialysis in the study group as a whole, a further analysis suggested that high-flux dialysis decreased cardiac death in the entire cohort and decreased all-cause mortality in patients who had been on long-term dialysis. This analysis was suggestive of a possible benefit but insufficient on its own to make the recommendation in the guideline stronger. It should be noted here that the HEMO study was performed in the USA where large for-profit dialysis chains have a financial benefit in proving that low-flux dialysis is as good as the more expensive high-flux dialysis.

The MPO study

A second RCT is now available, namely the MPO study, which was published in December 2008. This study compared survival in 647 patients randomized between high and low flux. It was designed be more sensitive to the influence of treatment, compared to the HEMO study, by selecting patients with relatively greater mortality risk. This was achieved by studying incident patients I.e. those who are started fresh on dialysis) with a serum albumin ≤40 g/l whereas the HEMO study enrolled prevalent patients (which includes those who have newly started on dialysis but also others who have been of dialysis for a longer time with the overall average length of time on dialysis being 3.7 years. This meant that the HEMO study had potentially selected fitter patients. Effectively they had selected a group of survivors, a large number of whom had previously been treated by high flux. By enrolling only incident patients the MPO study avoided any confounding or hangover effects related to the membrane type used prior to the start of the study.

The MPO study found no significant difference in survival between high- and low-flux groups when all patients were included in the analysis. However, when considering only patients with serum albumin ≤4 0 g/l on enrolment, there was a significant 37% reduction in mortality risk in patients treated by high flux. Further analysis also demonstrated a significantly improved survival in patients with diabetes when treated by high flux. In addition there was a significant improvement in serum beta-2-microglobulin (See Amyloidosis explanation at the end of this appendix) levels in patients treated by high-, compared to low-flux membranes for the whole group.

Interpretation and evidence level. The MPO study provides high grade evidence that survival is improved by the use of high-flux membranes in high-risk patients (as identified by serum albumin ≤40 g/l). The evidence is also very strong for the effect of flux on reducing levels of serum beta-2-microglobulin. However the study only provides moderate or low grade evidence that high flux improves survival in diabetics and did not provide evidence that it improved

survival in other groups of patients or in the group as a whole.

In clinical practice the choice of low as opposed to high flux may be based on financial constraints of which the cost of ultrapure water is a component. Ultrapure water is required when using high flux dialysis. Therefore high flux dialysis should be recommended for patients at high risk and the only factor hampering the use of high flux in all patients is the small difference in cost between high- and low-flux filters in a limited group of patients and the cost of ensuring a supply of ultrapure water. As such, it makes sense to recommend using high flux in all patients, even if the evidence to support the use of high flux in patients with low risk is lacking.

Guidance and conclusion. The existing Guideline 2.1 should thus be replaced by: Synthetic high-flux membranes should be used to delay long-term complications of haemodialysis therapy in patients at high risk (serum albumin <40 g/l) In view of underlying practical considerations, and the observation of a reduction of an intermediate marker (beta-2-microglobulin), synthetic high-flux membranes should be recommended even in low-risk patients

Explanation of terms used in this section

Amyloidosis is a group of diseases in which a protein, called amyloid, builds up in the organs and tissues. The build-up may happen in a single organ (localized) or throughout the body (systemically). Amyloid deposits can affect any organ or tissue.

There are three major types of systemic amyloidosis:

- Primary amyloidosis the most common form, occurs when bone marrow produces too much of certain fragments of antibody proteins, which build up in the bloodstream and may be deposited in body tissues.
- Familial (hereditary) amyloidosis is a genetic form passed down in families that often affects nerves and kidneys.
- Secondary amyloidosis develops along with a chronic infections or inflammatory disease, such as tuberculosis or rheumatoid arthritis.

Localized amyloidosis is associated with aging, as the body seems to naturally make amyloid as it ages. Two common conditions associated with localized amyloidosis are type 2 diabetes (where protein builds up in the pancreas) and Alzheimer's disease (where protein builds up in the brain). Beta2-microglobulin amyloidosis occurs in people with kidney failure who have been on dialysis for a long time (beta2 -microglobulin is a protein that can build up in the blood as a result of kidney failure).

Hyperphosphataemia means having too much phosphate in the blood. Often, calcium levels are lowered (hypocalcaemia) due to the combination of phosphate with the calcium which is then precipitated as calcium phosphate in tissues. There are 3 causes:

- Hypoparathyroidism: In this situation, there are low levels of Parathyroid hormone (PTH). PTH normally inhibits renal reabsorption of phosphate, and so without enough PTH there is more reabsorption of the phosphate.

- Chronic renal failure: When the kidneys aren't working well, there will be increased phosphate retention.
- Osteomalacia, which may be caused by the insufficient content of vitamin D in the diet, the lack of sunlight, malabsorption or renal disorders.