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Original Article

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High-flux or low-flux dialysis: a position statement following publication of the Membrane Permeability Outcome study

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Aim and scope

The European Renal Best Practice (ERBP) Advisory Board recently decided to follow up existing guidelines, and to publish position statements when new evidence would necessitate a change in the existing guideline [1].The purpose of this document is to provide guidance on the interpretation and relevancy of the current European Best Practice Guideline (EBPG) on dialysis strategy [2], in the light of the recently published Membrane Permeability Outcome (MPO) study [3].This position statement is intended to be considered in conjunction with the current guideline. It does not replace the guideline as we do not include a new systematic review of the literature. The MPO study specifically focused on the question whether the use of a high-, compared to a low-flux dialyser membrane, would have a measurable effect on survival.

Current guideline

The current European guideline relating to dialyser membrane permeability or flux is contained in the EBPG guideline on dialysis strategies [2], published in 2007. This document contains the following recommendation:

> Guideline 2.1: The use of synthetic high-flux membranes should be considered to delay long-term complications of haemodialysis therapy. Specific indications include: to reduce dialysis-related amyloidosis (level III); to improve control of hyperphosphataemia (level II); to reduce the increased cardiovascular risk (level II); to improve control of anaemia (level III).

At the time the guideline was prepared, there was insufficient evidence available to link membrane permeability with survival. This lack of evidence is reflected in the wording of the guideline, which mentions only relatively soft or surrogate outcomes such as anaemia, hyperphosphataemia, etc. The evidence for improved phosphate control is controversial. The wording 'should be considered', is, in effect, a level II (weak) recommendation. The evidence regarding the outcomes are moderate or weak (levels II or III) according to the grading system used in the guideline.

The guideline cites the Hemodialysis (HEMO) study [4] as the only randomized clinical trial (RCT) available which addressed the influence of high-flux dialysis on survival directly. This study found no difference in survival between high- and low-flux in the study group as a whole. However, post hoc, subgroup 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 subgroup analysis was considered to be suggestive of possible benefit, but insufficient on itself to make the recommendation in the guideline more strongly.

The MPO study

There is now a second RCT available, the MPO study [2], published in December 2008.

The MPO study compared survival in 647 patients randomized between high and low flux, and who completed the study. The study was designed to have increased sensitivity 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 with a serum albumin ≤40 g/l [2]. The HEMO study enrolled prevalent patients, who had been on dialysis for an average of 3.7 years, effectively being a group of selected survivors, a large part of whom had been treated by

high flux before. By enrolling only incident patients, the MPO study, thus, also avoided confounding or hangover effects related to the membrane type used prior to the start of the study. Numerous studies have shown that low serum albumin is associated with multiple adverse factors (e.g. malnutrition, inflammation, vascular disease) as well as increased mortality risk.

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 ≤40 g/l on enrolment, there was a significant 37% reduction in mortality risk in patients treated by high flux. Post hoc subgroup analysis demonstrated significantly improved survival in patients with diabetes when treated by high flux. There was a significant improvement (reduction in the rate of increase) in serum beta-2-microglobulin levels in patients treated by high-, compared to low-flux membranes for the whole group.

Interpretation and evidence level

The MPO study was designed to test the hypothesis that high flux improved outcome in patients with low serum albumin. Patients with normal serum albumin were added as a separate group in order to increase numbers while the study was underway. The normal and low albumin groups were separately randomized [5].

The MPO study provides level A (high grade) evidence that survival is improved by use of high-flux membranes in high-risk patients as identified by serum albumin ≤40 g/l. The evidence level is also A for the effect of flux on serum beta-2-microglobulin. The MPO study provides level B or C (moderate or low grade) evidence that high flux improves survival in diabetics as this is a secondary subgroup analysis. The MPO study did not provide evidence for high flux improving survival in other groups of patients or in the group as a whole.

In clinical practice, preference of low *vs* high flux can be based on financial restraints, and the need of ultrapure water when using high flux. As assuring water quality is a centre-specific item, and high flux should be commended in patients at risk based on high-grade evidence, the only factor hampering the use of high flux in all patients is the small difference in cost between a high- and a low-flux filter in a limited group of patients. 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 MPO study does not undermine the current guidance which suggests preferential use of high-flux membranes in all patients. The ERBP Advisory Board considers that the MPO study provides sufficient evidence to upgrade the strength of the guidance to a level 1A (strong recommendation, based on high-quality evidence) that high-flux dialysis should be used in the case of high-risk patients (comparable to the low-albumin group of the MPO study). In view of the small incremental extra cost of high-flux filters, the high prevalence of albumin <40 g/l at start of dialysis, and the substantial improvement in an intermediate marker (beta-2-microglobulin) in the high-flux group of the MPO study, the ERBP Advisory Board considers that expanding the use of high flux to all patients makes sense. The recommendation to use high flux in all patients remains at 2B (weak recommendation, based on moderate quality evidence).

The existing Guideline 2.1 should thus be replaced by the following:

> Guideline 2.1: 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) (level 1A: strong recommendation, based on high-quality evidence). 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 (level 2B: weak recommendation, low quality evidence).

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