High-flux or low-flux dialysis: A position statement following publication of the Membrane Permeability Outcome (MPO) study.

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European Renal Best Practice advisory Board:

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. The purpose of this document is to provide guidance on the interpretation and relevancy of the current European Best Practice Guideline on dialysis strategy, in the light of the recently published MPO study. 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, 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 wording “should be considered”, is, in effect, a level 2 (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 HEMO study as the only 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, sub-group analysis suggested that there may be improved
survival due to high-flux in patients with high co-morbidity. This sub-group analysis was considered to be
suggestive of possible benefit, but insufficient on itself to make the recommendation in the guideline
more strongly. It was noted that the HEMO study was under-powered to detect clinically relevant
differences in mortality between groups since insufficient deaths would be expected during the study.

The MPO study

There is now a second RCT available, the MPO study, 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≤4 g/dl. 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 hang-over 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 ≤4
g/dl on enrollment, there was a significant 37% reduction in mortality risk in patients treated by high-
flux. Post-hoc sub-group 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 low-albumin group was part of the initial MPO study design and prospectively declared. For this
reason, findings for this group should be considered as level A (high grade) evidence. Patients with
normal albumin (>4 g/dl) were only enrolled after the inclusion criteria were widened while the study
was under way. Only 30 out of a total of 162 observed deaths occurred in the normal albumin group.
The inclusion of patients with normal serum albumin was not part of the original study design but was
considered a pragmatic necessity in order to recruit sufficient subjects.
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 ≤4 g/dl. The evidence level is also A for the effect of flux on serum beta-2-microglobulin. The MPO study did not provide level A evidence on survival in patients other than those with serum albumin ≤4 g/dl but it was not designed or powered to do so. The MPO study provides level B or C (moderate or low grade) evidence that high flux improves survival in diabetics.

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 <4g/dl at start of dialysis, and the substantial improvement in an intermediate marker (Beta2 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 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 risk (serum albumin<4g/dl)(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 (Beta2 microglobulin), synthetic high flux membranes should be recommended even in low risk patients (level 2B: moderate recommendation, low quality evidence).

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References


