EDITORIAL

Is There an End in Sight for Encapsulating Peritoneal Sclerosis?

Encapsulating peritoneal sclerosis (EPS) was first described by Gandhi *et al.* (1). Encapsulating peritoneal sclerosis carries high morbidity and mortality due to abdominal pain and nutritional problems. The mortality from this condition has been estimated to be 50%, although better results have been recently reported from tertiary surgical centers (2).

Epidemiological studies have been derived from various registries such as Scottish, Pan-Thames (south-east England), Netherlands, Australia-New Zealand, and Japan (3–6). There is consensus that EPS is very rare in people who were on peritoneal dialysis (PD) for less than 3–4 years. For those with PD exposure below 1 year, the incidence approaches 0, and for those below 3 years, it is less than 1%. However, the percentage steadily rises as the duration of PD goes beyond 3–5 years (8% being at the high end; Scottish Registry (4)).

There is the golden truth that prevention is better than cure. To “prevent” this disease, should we limit PD exposure to our patients (e.g. to 5 years)? This question was addressed in a Position Statement by the International Society of PD (ISPD) (7) and concludes that there is not enough evidence to withhold PD because of the fear of EPS, nor should there be a single rule about optimal length of time on PD to avoid the risk of EPS.

The subtext of the ISPD position statement is:

- 1) Can we identify an “at risk” group with greater sensitivity and specificity than using PD vintage alone?
- 2) Other than discontinuing PD, are there other treatment strategies?

The study published in this journal by De Sousa *et al.* (8) is welcome as it directly addresses these 2 points. The authors have defined “EPS-prone” patients as having at least 2 of the following:

- 1) PD vintage > 3 years
- 2) Recurrent or “severe” peritonitis
- 3) “Severe” hemoperitoneum
- 4) Overexposure to glucose

- 5) Evidence of acquired ultrafiltration failure (UFF) or “high/fast” peritoneal membrane transport status

The authors have proceeded to treat the EPS-prone patients with:

- 1) Temporary or definitive cessation of PD
- 2) Oral tamoxifen 20 mg/12 h for 1 year

The authors compared the incidence of EPS before and after introduction of their protocol to identify and prevent EPS. Whilst most clinicians would agree that these factors used to define “EPS-prone” are sensible, the authors’ classification has not been previously validated. Strictly speaking, the authors should have validated whether the “EPS-prone” group is at higher risk of developing EPS; otherwise, their treatment protocol is irrelevant and any reduction in EPS rates would be due to other changes in clinical practice that inevitably occur over 3 decades. With this caveat, one must acknowledge that the results reported are striking: all 14 pre-emptively treated at-risk patients (identified over a 15-year period) who were treated with tamoxifen (including 9 who ceased PD) were free from EPS at the end of the study. This has led to an EPS incidence of only 0.3% of patients starting PD after 2000. By contrast, the incidence of EPS in the same unit was 5.6% for patients starting PD between 1980 and 1990 and 3.9% for patients starting PD between 1991 and 2000.

These findings have particular relevance; the authors’ own animal and basic science studies support the theoretical use of tamoxifen. Several studies have demonstrated that tamoxifen may influence the epithelial-to-mesenchymal transition and fibrosis of mesothelial cells (9). Should there be more widespread adoption of the protocol described by De Sousa? The authors are correct to emphasize caution and list the limitations of their study.

Given the very widely stated diagnostic criteria for EPS-prone, one suspects that other clinical suspicions were required. Over 15 years, to have only 7 cases of “severe” or recurrent peritonitis would be the envy of many. Moreover, the correlation between UFF/transport status and high glucose usage would mean anyone with high/fast transport status would be likely to be “EPS-prone.” The literature would suggest that

approximately 20% of incident patients on PD are fast transporters (10,11). However, defining these "suspicions" can be difficult and often relies on senior clinical judgment. The collaborative European EPS registry (www.epsregistry.eu) and the Global Fluid Study (12) are promising platforms that permit necessary data collection from which one hopes more objective and specific diagnostic criteria (perhaps changes in peritoneal biomarkers or a constellation of demographic and clinical metrics) can be derived.

By coincidence, another recent study by Goodlad *et al.* (13) published in this journal showed dialysate cytokines did not improve prediction of EPS above clinical risk factors. Using just 2 factors, PD vintage and peritoneal membrane transport characteristics (dialysate/plasma creatinine ratio, D/Pcr), area under the receiver operator characteristics curve was 0.886 (generally considered good for a diagnostic test). In the De Sousa study, 11 of the 14 "EPS-prone" patients had high D/Pcr (or UFF) but only 8 of 14 had PD vintage > 3 years. It is, therefore, unclear how many of the patients in this study fulfilled the "Goodlad" criteria for predicting EPS. De Sousa *et al.* switched 9 of the 14 patients to hemodialysis (HD) after the diagnosis of "EPS-prone." A discussion about elective switching would be eminently sensible in patients with prolonged PD vintage who acquire high peritoneal membrane transport; not only to "prevent" EPS but because PD technique failure is high. One hopes that early preparation of arterial-venous fistulae may reduce "crash-landing on HD" and minimize morbidity during the transition.

Irrespective of the criteria to diagnose "EPS-prone," should we prescribe tamoxifen more widely in the expectation that it will reduce the incidence of EPS? A retrospective study of 63 EPS patients reported a lower mortality in the tamoxifen-treated group (14). The authors concluded that due to the morbidity and short life expectancy of EPS patients, the benefits from this therapy outweighed the risks (tamoxifen is associated with thromboembolism, strokes and endometrial carcinoma (15)). But this balance of risk may not apply to EPS-prone patients with long life expectancy and who may never develop EPS. A majority of the papers reporting about the use of tamoxifen did not report any of these adverse events, but the true risk of treatment might be difficult to ascertain from small retrospective studies. Also, any benefits seen in the intervention by De Sousa *et al.* may be due to modality switch to HD, and the effect of tamoxifen to reduce the progression of disease is unclear.

Determination of the risk/benefit ratio also requires us to know how effective tamoxifen will be at preventing

EPS. Whilst the report by De Sousa is highly encouraging, some circumspection is required; although none of the 14 EPS-prone patients developed "full blown" EPS, 2 subsequently presented with small bowel obstruction and 1 with small bowel perforation. Moreover, the median follow-up of these patients was 54 months and the study design meant that some would have had very short follow-up. The authors have already acknowledged that there may be other confounding factors that have led to a reduced incidence of EPS but another confounder may be differential rates of transplantations and thresholds for switching to HD; these would mean that the time on PD for the more recent cohort of patients may be lower than for the historical controls.

Preventing EPS with early interventions is an exciting and very promising topic. Intuitively, the approach taken by the authors of the study feels correct; identify the patients at risk and pre-emptively treat them with a relatively well-tolerated medication. But there are still many unanswered questions; what criteria should we use to diagnose "EPS-prone" and how safe is tamoxifen? I congratulate the authors on this useful study that should precipitate debate and reflection on how we manage long-term PD patients. I can only concur with the authors, "Additional well-planned studies are needed."

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