Dialyzer First Use Reaction with Polysulfone Membrane: Moving Beyond Ethylene Oxide

Abstract

Acute anaphylactic/anaphylactoid reactions to dialyzers are uncommon. Indeed, they are thought to have decreased in incidence since the transition to more biocompatible dialyzer membranes and with the abandonment of ethylene oxide for sterilization of dialyzers. However, few recent Spanish studies suggest that the incidence actually remains the same. Here, we report two cases of dialyzer first use reactions that occurred with polysulfone dialyzers. These were not ethylene oxide sterilized dialyzers and the reactions were less intense/absent from the second reuse onwards. Both the patients were successfully dialyzed by switching to a cellulose triacetate dialyzer or by using a preprocessed dialyzer filled with renalin. Thus, the cause of the reaction could either be the primary polysulfone membrane or a leachable substance from the dialyzer.

Keywords: Anaphylaxis, Dialysis, polysulfone, reaction

Introduction

Acute anaphylactic/anaphylactoid reactions to dialyzers are uncommon. Indeed, they are thought to have decreased in incidence since the transition to more biocompatible dialyzer membranes and with the abandonment of ethylene oxide for sterilization of dialyzers. However, few recent Spanish studies suggest that the incidence actually remains the same. Here, we report two cases of dialyzer first use reactions which occurred with polysulfone dialyzers. These were not ethylene oxide sterilized dialyzers and the reactions were less intense/absent from the second reuse onwards. Surprisingly, these reactions did not recur when a new polysulfone dialyzer was used after it had been subjected to the usual reuse protocol with renalin. Thus, the cause of the reaction could be either the primary polysulfone membrane or a leachable substance from the dialyzer.

Case Reports

Patient 1

A 55-year-old lady with long standing hypertension, gout and chronic kidney disease who has been on hemodialysis via AV fistula since March, 2018 with F6HPS dialyzer (Fresenius, Polysulfone membrane, steam sterilized) with no untoward effects at initiation.

From June 2018 onwards (i.e., 3 months after starting dialysis and 26th dialysis onwards) she was noted to have intermittent episodes of chest tightness, back pain and breathlessness after 30-60 minutes of starting HD. Dialysis sessions had to be terminated early on a few occasions but mostly these symptoms subsided on continuing dialysis. She did not have fever, pruritus, hypotension or loss of consciousness. Preliminary evaluation including counts, Chest X Ray, ECG and cardiology evaluation including ECHO and Cardiac enzymes were normal. These symptoms persisted despite adequate BP control and even after reduction of dry weight. The reactions occurred infrequently and a pattern was recognized only after 2 months. It was noticed that these reactions were limited to the first dialyzer use and there were no symptoms on subsequent reuse of the same dialyzer.

An acute dialyzer reaction was suspected which did not recur with re-use, which can thus qualify as a ‘first use’ reaction. Eosinophil counts were normal but serum IgE levels and serum tryptase levels were borderline high [Table 1]. Since dialyzers with alternative membranes like cellulose triacetate were not available,
Tharakan: Dialyzer reaction with polysulfone membrane

Table 1: Laboratory reports

| Pre event | Post Event |
|-----------|------------|
| **1TLC** | **2DLC** | **1TLC** | **2DLC** | **S.IgE (IU/ml)** | **S.Total Tryptase (µg/L)** |
| Case 1   | 6600 (30 days prior) | $N_{22}^1-E_{21}$ (30 days prior) | 7200 (After dialysis on same day) | $N_{22}^1-E_{21}$ (After dialysis on same day) | 166 (After dialysis on same day) | 14.7 (After dialysis on same day) |
| Case 2   | 8400 (50 days prior) | $N_{22}^1-E_{21}$ (50 days prior) | 7300 (Next day) | $N_{22}^1-E_{21}$ (Next day) | >1000 (Next day) *Not done |

1Total leucocyte count, 2Differential leucocyte count

Different dialyzers from the polyarylsulfone family were tried including ELISIO150LR (Nipro, polysulfone, gamma sterilized) and Pristine BD 130 (Browndove, polyethersulfone, gamma sterilized). Similar reactions occurred with these dialyzers. Predialysis steroids and antihistaminics were tried but were ineffective. Since the patient was not willing to shift to peritoneal dialysis, we were forced to continue dialysis with available dialyzers. We noticed that subjecting all new dialyzers to reuse protocol by filling with renalin 24 h prior to first use resulted in a symptom free dialysis. We continued dialysis with F6HPS dialyzer in this manner and there was no further incident for the next 6 months.

However, in Dec, 2018 (6 months later) she developed breathlessness and chest tightness while on F6HPS dialyzer, that was similar to previous episodes. It was found that the dialysis nurse had forgotten to flush the new dialyzer with renalin before first use. This accidental re-challenge confirmed acute first use reaction to F6HPS dialyzer. She continues dialysis till date (close to a year) without any further reactions. Clinical details have been summarized in Table 2.

**Patient 2**

A 65-year-old male with type 2 diabetes mellitus, hypertension and chronic kidney disease was on hemodialysis via AV fistula since June 2019 with F6HPS dialyzer (Fresenius, Polysulfone membrane, steam sterilized). He had history of bronchial asthma during early adulthood, currently asymptomatic and off bronchodilators/steroids.

In August, 2019 he developed sudden onset loss of consciousness with hypotension few minutes after starting dialysis (New F6HPS Dialyzer). It was his 16 th dialysis session. There was spontaneous recovery on stopping dialysis. Dialyzer had to be discarded due to clotting. Cardiology evaluation including ECG, Cardiac enzymes and ECHO heart were normal. Hemodialysis was attempted the next day (while on Holter) with a new F6HPS dialyzer, when he developed breathlessness, chest tightness and hypotension again, few minutes after initiation and which was relieved instantaneously upon stopping dialysis. Since it occurred immediately after starting dialysis with a new dialyzer, an acute dialyzer reaction was suspected and dialysis was restarted with a different dialyzer Pristine BD 130 (Browndove, Polyethersulfone, gamma sterilized) with same effect. We then attempted dialysis with a non-polysulfone membrane- Cellulose Triacetate Membrane dialyzers (CTA 2000, Kawasaki) with which there was no reaction, confirming an acute dialyzers reaction to polysulfone dialyzers. Serum IgE levels were found to be greater than 1000 with peripheral blood eosinophilia suggestive of an anaphylactic reaction [Table 1]. Serum tryptase was not done. Subsequent dialysis with CTA 2000 dialyzer were uneventful. As we did not have further stock of CTA membrane dialyzers, we attempted dialysis after filling the available dialyzers with renalin prior to first use. Fortunately, he did not develop a reaction to the same. He continued dialysis with us for the next two months uneventfully before being transferred to another center. Clinical details have been summarized in Table 2.

**Discussion**

Dialyzer reactions are rare but not uncommon and we should always be alert to this possibility during a hemodialysis setting. Earlier, bioincompatible membranes and ethylene oxide used for sterilization of dialyzers were the most common causes. The nephrology community has moved on to using polysulfone membranes and ethylene oxide is rarely ever used for sterilization of dialyzers. It is the general feeling that with these two changes dialyzer reactions have become rare. However, various studies show that despite the changing trends in dialyzer membranes and the mode of sterilization the incidence of dialyzer reactions remains the same. In 1987, Nicholls et al. described an incidence of 2-5% of dialyzer reactions in UK. In 1996, nearly a decade later, Simon described an incidence of 2.1% among 1536 patients from 30 dialysis centers in France. Use of ethylene oxide for sterilization of dialyzers showed a decreasing trend and the more biocompatible polysulfone membranes became more widely used since the turn of the century. However, in 2018, Esteras et al. in a retrospective study in Spain across nine dialysis centers, found 37 (2.37%) reported cases out of 1561 patients in a two year period form August 2015 to August 2017 which is the around the same incidence as the two earlier described studies done more than 20 years back. Most of the reported reactions, after the year 2000, have been to polysulfone membranes, which is unsurprising, as it is the most widely used membrane now-a-days. Boer et al. reviewed 32 cases
of dialyzer reactions which were found to be mostly due to polysulfone membrane dialyzers which were managed by switching to cellulose triacetate membrane dialyzer. There have been very few reports of dialyzer reactions from India. A case of hemodialysis intolerance and eosinophilia was reported by Nayak-Rao in 2015 from Bangalore. It is likely that these reactions are under reported or being missed.

The two cases which we have described above were reactions to polysulfone dialyzers which were steam sterilized. These reactions did not occur at initiation of dialysis but occurred after many weeks on the same type of dialyzer. Boer noted in his review that dialyzer reactions may manifest more than a year after starting dialysis. Interestingly, polysulfone membrane dialyzers could still be used if the dialyzer was filled with renalin prior to first use. Since ethylene oxide is not used currently for sterilization of dialyzers these reactions are likely to be due to some other component of the dialyzer. It may not be the primary membrane material itself but a leachable substance from the dialyzer which causes the above reaction. Alternatively, renalin could have rendered a potential hypersensitivity causing allergen inactive. Molecules like polyvinylpyrrolidone, bisphenol A, parabens, carbamates, thiurams, formaldehyde, rubber, plastics, epoxy resins can trigger hypersensitivity reactions. More research is needed as to find the actual cause of these first use reactions which may not be seen with cellulose triacetate membrane dialyzers.

The obvious choice when encountering a possible hypersensitivity reaction to polysulfone membrane-based dialyzers is to switch to cellulose triacetate membranes. However cellulose triacetate membrane dialyzers are very difficult to procure in India. Till they are made available, an alternative would be to attempt hemodialysis again with renalin pre-filled dialyzers and rigorous priming prior to first use in any patient suspected to have a hypersensitivity reaction, especially if they are not willing to shift to peritoneal dialysis.

**Conclusion**

Even though dialyzer reactions are rare we need to stay alert to its possibility. Acute dialyzer reactions still occur even though ethylene oxide is no longer used for sterilizing dialyzers and most of the dialyzers in use are ‘biocompatible’ polysulfone based dialyzers. They can even be delayed by many months. However, emergency dialysis may be attempted with a renalin pre-filled new dialyzer after rigorous priming if there is no other alternative.

**Declaration of patient consent**

The author certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Nicholls AJ. Hypersensitivity to hemodialysis: The United Kingdom experience. Artif Organs 1987;11:87-9.
2. Simon P, Potier J, Thebaud HE. |Risk factors for acute

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**Table 2: Summary of clinical features and treatment**

| Symptoms                   | Onset            | Access   | Dialyzer     | Treatment                                                                 |
|---------------------------|------------------|----------|--------------|---------------------------------------------------------------------------|
| Case 1 Chest tightness,   | More than 3      | AV       | F6HPS (Steam | Dialysis continued.                                                        |
| back pain, breathlessness,| 30 to 60 min     | fistula  | sterilized)  | ¹Switched to Polysulfone dialyzers from other manufacturers-Reactions recurred. |
| vomiting                  | after starting   |          |              | ²Pre-processed F6HPS dialyzer tried (Cellulose triacetate dialyzer not available)- No Reaction. |
|                          |                  |          |              | ³Rigorous priming (Not effective alone).                                    |
|                          |                  |          |              | Predialysis steroid/antihistaminic injection (Not effective alone).        |
| Case 2 Hypotension,       | Within minutes   | AV       | F6HPS (Steam | Dialysis stopped.                                                          |
| Breathlessness, Chest     | of starting      | fistula  | sterilized)  | ¹Switched to Polysulfone dialyzers from other manufacturers-Reactions recurred. |
| tightness                 |                  |          |              | ²CTA 2000 dialyzer-No Reaction.                                           |
|                          |                  |          |              | ³Pre-processed F6HPS dialyzer (Since only one cellulose triacetate dialyzer was available) -No reaction. |
|                          |                  |          |              | ³Rigorous priming (Not effective alone). Predialysis steroid/antihistaminic injection (Not effective alone). |

¹ELISIO150LR (Nipro), Pristine BD 130 (Browndove), ²New F6HPS dialyzer filled with disinfectant (Renalin) at least 24 h prior to first use, ³Priming with more than 3 liters of saline, ⁴CTA 2000-Cellulose triacetate dialyzer (Kawasumi, Japan)-only single dialyzer was available. Discarded after 8 reuses and then switched to pre-processed F6HPS dialyzer. Other vendors for cellulose triacetate dialyzers required minimum order of 24 dialyzers and 3 months’ time for import.
hypersensitivity reactions in hemodialysis]. Nephrologie 1996;17:163-70.
3. Esteras R, Martin-Navarro J, Ledesma G, Fernández-Prado R, Carreño G, Cintra M, et al. Incidence of hypersensitivity reactions during hemodialysis. Kidney Blood Press Res 2018;43:1472-8.
4. Boer WH, Liem Y, de Beus E, Abrahams AC. Acute reactions to polysulfone/polyethersulfone dialysers: Literature review and management. Neth J Med 2017;75:4-13.
5. Nayak-Rao S. A patient with hemodialysis intolerance and hypereosinophilia. Saudi J Kidney Dis Transpl 2015;26:366-7.