Historical Milestones in Peritoneal Dialysis

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Abstract

Two and a half centuries have passed since the therapeutic use of peritoneal cavity for the treatment of ascites by peritoneal lavage was reported. George Ganter was the first to describe the use of peritoneal dialysis (PD) in humans. This chapter will describe the various milestones in the field of PD achieved over the years. These include the understanding of solute and water transport across the peritoneal membrane, developments in PD technique and technology, progress in the prevention and treatment of infections, and other important milestones.

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The concept of peritoneal dialysis (PD) as a possible mode of renal replacement therapy is almost a century old. This chapter will trace the origins of PD from its early days and subsequently describe the various historical milestones achieved since its inception to the present day under the following subheads:

- The peritoneal membrane/cavity as a therapeutic tool
- PD solutions (PDS)
- PD technique evolution
- The birth of continuous ambulatory PD (CAPD)
- Introduction of Y set in PD
- PD dose
- Unplanned and urgent start PD

The Peritoneal Membrane/Cavity as a Therapeutic Tool

Rene Dutrochet was the first to describe the process of osmosis in the 18th century. This was later followed by Thomas Graham's (19th century) description of the difference between "crystalloids" and "colloids" in his "Bakerian lecture on osmotic forces" [1, 2]. In the late 19th century, Clark, Orlo and Wegner demonstrated that the instillation of hypertonic solution (salt, concentrated sugars, glycerol) in the peritoneal cavity increases the peritoneal cavity volume in animal experiments [3]. The evidence for "bi-directional permeability" (blood to peritoneal cavity and vice-versa) of the peritoneal membrane was provided later by Babb et al. [4]. Based on the transport behavior of solutes like methylene blue, Putnam's description of the peritoneum as a membrane with "punched out holes" that allowed larger molecules (now interpreted as middle molecules) to pass through, later helped in the understanding of the mechanism of large solute removal by PD [3]. Advances in cell biology and advent of electron microscopy subsequently led to the emergence of the 3-pore theory; including the recognition of the role of aquaporins [5]. Interestingly, the prediction that the water transport across the peritoneal membrane occurred via transcellular pathways had already been made earlier [6].

PD Solutions

It was recognized early on that to remove uremic solutes effectively, a hypertonic solution will need to be instilled in the peritoneal cavity. The early PD solutions led to adverse events like post instillation pain (due to lack of acetate/lactate resulting in low Ph), hyperchloremic metabolic acidosis, volume overload, and hypertension [7], were mainly related to higher concentration of sodium in these solutions (Na and Cl concentration of 136 mEq/L). Subsequent formulations of PDS were appropriately modified in an effort to make them more physiological as well as to promote sodium removal by diffusion (sodium 130–135 mEq/L, chloride 99–100 mEq/L). Heusser [3] recognized that dextrose could be utilized as an osmotic agent to achieve ultrafiltration in the PDS. Although many other agents (e.g., glycerol, amino acids etc.) have since been tried, dextrose continues to be the preferred osmotic agent in the PDS. However, prolonged exposure to dextrose is associated with several unwanted effects that include hyperglycemia and new onset diabetes mellitus, weight gain, and dyslipidemia [8]. Also, prolonged exposure to dextrose can adversely affect the peritoneal membrane causing mesothelial toxicity, neo-angiogenesis, and formation of advanced glycosylation end products leading to loss of ultrafiltration and other adverse sequelae [9].

Table 1. Advantages of biocompatible solutions

Icodextrin
pH 5.8, iso-osmotic 7.5% high-molecular-weight glucose polymer
Provides sustained ultrafiltration (similar to "colloid" osmosis) with the long dwell
Better glycemic, lipid volume and blood pressure control
Glucose-sparing agent, less GDP exposure
1.1% amino acid
Glucose-sparing agent, less GDP exposure
Used in malnourished patients, replenishes 18 g per day of protein (one 2 L exchange/day)
Lactate/bicarbonate buffered solution
pH 7.4 and less instillation pain, less lactate, less GDP exposure, less peritonitis

PDS contain lactate as the buffer. The use of lactate (pH 5.5) buffered PDS has been implicated with in-flow pain. The stimulation of the polyol pathway by lactate may enhance glucose-related mesothelial cell toxicity [9]. PDS are heat-sterilized prior to use. Heat sterilization results in the production of glucose degradation products that are cytotoxic to the peritoneal membrane. The need for more biocompatible PDS (with lower proinflammatory profile and lower propensity to cause changes in peritoneal structure, function, and defense mechanisms) thus became increasingly apparent.

Since their introduction, biocompatible PDS have been widely used in Europe but they have not been available in the US with the exception of Icodextrin (7.5%), which was introduced in the 1990s. The 1.1% amino acid solution, lactate and lactate/bicarbonate buffered solution are some of the other biocompatible PDS [9] (Table 1).

Longer PD vintage predisposes to structural and functional changes of the peritoneal membrane resulting in ultrafiltration failure and reduced solute clearance, ultimately resulting in technique failure. The recognition of transforming growth factor β 1 as a target molecule to reduce peritoneal fibrosis has led to the use of agents like aminoguanidine, pyridoxamine, pentoxifylline, diltiazem, and dipyridamole. In this context, the reported utility of renin-angiotensin aldosterone blockers in the prevention of peritoneal fibrosis is noteworthy [9, 10].

PD Technique Evolution

Georg Ganter was the first to study the effects of instilling hypertonic saline in 2 cases with renal failure [1]. Heusser and Wegner attempted peritoneal lavage with 2 catheters (inflow and outflow) for mercury poisoning but despite biochemical improvement, the patients ultimately died [1]. World War II brought

with it a tsunami of crush injuries associated acute renal failure with very high mortality rate. In 1946, encouraged by their adaptation of the Wegner continuous flow technique and painstaking attention to sterility, Frank, Seligman and Fine from Boston reported renal recovery and eventual survival of an anuric acute renal failure patient after 4 days of peritoneal lavage. Approximately, 150 cases of acute renal failure were subsequently treated in such manner, although mortality remained very high [3].

Early investigators used 2 catheters in PD: one as an inflow catheter between the diaphragm and liver, and the other for outflow, in the lower peritoneal cavity. The peritoneal lavage was thus continuous in nature. This technique was associated with several complications including leakage of PD solution and infections resulting in high mortality. As a result, this practice was quickly abandoned and the technique using a single catheter for both inflow and outflow (hence the term intermittent) was adopted. It should be noted that the current terminology differentiates continuous and intermittent PD based on the presence or absence of PD solution within the peritoneal cavity for a continuous or intermittent period. For example, intermittent PD has “dry periods during a 24-h time frame during which there is no solution in contact with the peritoneal membrane.

Peritoneal access remained a major challenge in the early days of PD. Different materials and prototypes were tried including Foley catheters, mushroom tip catheters, whistle tip catheters, polyethylene tubes, simple soft rubber tubes with or without side holes, stainless steel sump drains (similar to the metal-perforated suction tubes, used in operating theatres) and even glass drains [11, 12]. Leakage and intraluminal or extraluminal obstruction limited their use, and since the catheter needed to be changed repeatedly over few days, infection risk remained high. It was not until 1950s and 1960s, when investigators like Maxwell, Doolan, Weston and Roberts [3] modified the catheter and improved insertion techniques that the benefit to risk ratio swayed towards PD compared to standard conservative or supportive therapy for acute renal failure. Despite this, the need for repeated intermittent access to abdomen remained a big challenge [12, 13]. The concept of “closed loop circuit” involving storage of PDS in closed containers (as opposed to open containers with open circuits) was introduced by Frank, Seligman and Fine. In this system, the fluid was siphoned out into an airtight container, thus, minimizing the chances of infection. Soon, further modification of this system lead to “hanging bottle system” by Doolan and Maxwell, facilitating the commercial production of PDS [3].

During this time, PD was offered exclusively as in-hospital modality (often offered as a last resort to patients who were not candidates for extracorporeal treatment). A typical “treatment” included instillation of PDS manually by nursing staff several times during the day (requiring multiple changes of entire sets),

thus risking contamination and subsequently peritonitis. The first use of PD in ESRD patient was reported in the late 1950s. The patient felt better after just 1 day of treatment. PD was therefore continued on as needed basis with frequent monitoring of plasma chemistry. This patient survived for 6 months after which she decided to discontinue the treatment and passed away [3]. Despite the initial success, long-term PD was frequently associated with recurrent episodes of peritonitis. This, together with the inability to gain permanent access to the abdomen slowed its widespread use. In the 1950s and early 1960s, Normal Deane introduced a prosthesis that was used to keep the catheter track patent in between treatments. This prosthesis represented a significant improvement in the care of these patients, thus obviating the need for recurrent catheter insertion with attendant risk of perforation. Instead the patient would come to the unit twice a week and a stylet catheter was slipped through the permanent track after removal of the Deane's prosthesis. Oreopoulos et al. [2] used this method in about 40 patients over 2–3 years.

Introduction of the Tenckhoff catheter in 1968 is considered a paradigm shift in the use of PD for ESRD patients. The original Tenckhoff catheter was made from Silastic and represented a technical modification of the curled Palmer catheter. It had an open end and numerous side holes in its terminal part. The 2 Dacron felt cuffs offered protection against infection along the subcutaneous tract: one just outside the peritoneum, and the other in the subcutaneous tissue. The curled section of the Palmer catheter was replaced by a straight intra-abdominal part. Description of various modifications of the original Tenckhoff catheter is beyond the scope of this book but can be found in an excellent review by Twardowski [13].

Another significant contribution towards providing PD as a home-based therapy was the introduction of the cyclor machines that could be programmed to provide multiple PD exchanges at home on several days of the week. A detailed description of cyclers will be discussed elsewhere in the book.

The Birth of Continuous Ambulatory PD

In 1978, based on their work on theoretical mass transfer, Popovich and Moncrief described a continuous form of PD known as portable/wearable equilibrium dialysis technique. The investigators cited good biochemical control and liberal dietary and fluid intake as major advantages of such a technique. Oreopoulos et al. [14] at Toronto Western Hospital were the first to use PDS supplied in plastic bags (instead of glass bottles originally used by Popovich and Moncrief). Following the availability of PDS in plastic bags, Oreopoulos et al. [14] from Toronto Western Hospital developed a meticulous protocol for CAPD.

Introduction of Y Set in PD

Italian investigators led by Umberto Buoncristiani were unable to reproduce lower peritonitis rates in their PD patients despite adopting the Toronto Western Hospital CAPD protocol. They subsequently observed that with the use of a “Y” set and “flush before fill” technique, the possibility of contamination occurring during the spiking of bags could be significantly reduced [15]. As a result of this technique, they noticed a significant reduction in peritonitis rates. Although it took several years for investigators to adopt the “Y-set,” it has proven to be the single most significant factor in preventing peritonitis in CAPD patients (from 1 every 3–4 patient-months to 1 every 30–35 patient-months) [15].

PD Dose

During early days of PD, the dose of PD was primarily determined by plasma chemistry, anemia indices, and clinical parameters. PD was often prescribed for 10 h for few days of the week. In the 1980s, Popovich-Pyle introduced the concept of mass transfer area coefficient that calculated the maximum theoretical clearance of a solute by diffusion [16]. In the 1990s, Haraldsson [17] re-examined urea kinetics in PD. This research was seminal in leading to the development of guidelines underscoring the minimal urea clearance necessary for PD, thus providing guidance on dialysis dosing in PD. Later, Bargman et al.’s [18] reanalysis of the CANUSA study highlighted the importance of residual renal function in determining patient outcomes in PD.

Over the last few years, there has been a re-emergence of the concept of incremental PD, it not only provides adequate dialysis but also emphasizes the importance of preservation of residual renal function and minimizes therapy burden [19]. Progressive loss of residual renal function adversely impacts the clearance of middle and large molecules. A majority of patients have to switch to hemodialysis once they become anuric. This is especially relevant in those on continuous PD with maximum prescribed fluid volumes. In this context, the concept of Continuous-Flow PD (CFPD), first described by Shinaberger et al. [20] becomes relevant. CFPD offers a mode of PD with a continuous flow-through of dialysate into and out of the peritoneal cavity. This technique requires either 2 PD catheters or a double-lumen catheter. Dialysate is infused through one port and is simultaneously drained from the second. Table 2 summarizes the advantages and disadvantages of this modality. Detailed reviews can be found elsewhere [21].

Table 2. Continuous-Flow Peritoneal Dialysis (CFPD): advantages and disadvantages, adapted from Ref. [21]

Advantages of CFPD	
	Continuous contact with dialyzer membrane due to no loss of therapy time, better solute clearance
	Maintenance of solute and osmotic concentration due to continuous replenishment of glucose
	Potential for online generation of dialysate with more biocompatible solutions
Disadvantages of CFPD	
	Shortened dwell time, lowering middle and large molecule clearance.
	Technologically challenging to provide large volumes of PDs

Unplanned and Urgent Start PD

Approximately, 30–40% patients (in North America, Europe) start dialysis without a functioning permanent access, that is, an arteriovenous fistula or a PD catheter. A sudden deterioration in renal function due to superimposed acute kidney injury with subsequent non-recovery, lack of in-depth discussions between the patients and nephrology team regarding “personalized best fit modality,” and inadequately functioning arteriovenous fistula at the start of hemodialysis lead to increased use of intravenous catheters for dialysis (a major determinant of morbidity and mortality in ESRD). Several studies across the world [22–24] have now shown success of “Urgent PD start” using low volume exchanges in supine position without waiting for the traditional 2-week catheter break-in period. Although peritoneal catheter leaks and mechanical obstruction continue to be a hurdle for success of this modality [25], several centers have shown close to 18–30% increase in PD utilization after the implementation of an “Urgent Start” program. In the USA, more programs are adapting to the idea of “Transitional Care Units” where the “crash starts with catheters” are provided assisted hemodialysis within the first few weeks in a separate unit. During this time, patients and their families are educated about the advantages and disadvantages of home-based therapies, resulting in increased uptake of PD [26]. In the US, significant efforts by nephrology community towards imparting knowledge of mechanics, procedures, and advantages of home dialysis has been achieved. Reinvigorated interest in home-based therapies, backed by financial incentives provided by the government, may continue to increase the PD utilization over the next several years [27].

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