Experimental models in peritoneal dialysis (Review)

BO YANG[1*], MENGMENG WANG[2*], XUE TONG[1*], GHADA ANKAWI[3], LIN SUN[1] and HONGTAO YANG[1]

[1]Department of Nephrology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300381; [2]Department of Endocrinology, Fuyang Fourth People's Hospital, Fuyang, Anhui 236000, P.R. China; [3]Department of Internal Medicine and Nephrology, King Abdulaziz University, Jeddah 21589, Saudi Arabia

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Abstract. Peritoneal dialysis (PD) is one of the most commonly used dialysis methods and plays an important role in maintaining the quality of life of patients with end-stage renal disease. However, long-term PD treatment is associated with adverse effects on the structure and function of peritoneal tissue, which may lead to peritoneal ultrafiltration failure, resulting in dialysis failure and eventually PD withdrawal. In order to prevent the occurrence of these effects, the important issues that need to be tackled are improvement of ultrafiltration, protection of peritoneal function and extension of dialysis time. In basic PD research, a reasonable experimental model is key to the smooth progress of experiments. A good PD model should not only simulate the process of human PD as accurately as possible, but also help researchers to understand the evolution process and pathogenesis of various complications related to PD treatment. To better promote the clinical application of PD technology, the present review will summarize and evaluate the *in vivo* PD experimental models available, thus providing a reference for relevant PD research.

Contents

Correspondence to: Dr Bo Yang or Dr Hongtao Yang, Department of Nephrology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 88 Changling Road, Tianjin 300381, P.R. China
E-mail: yangbotcm@foxmail.com
E-mail: tjtcmht@126.com

*Contributed equally

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Introduction

Peritoneal dialysis (PD) is one of the most commonly used dialysis methods in the clinic, and utilizes the nature of the peritoneum as a semipermeable membrane to exchange water and toxic solutes in the peritoneal cavity (1). Compared with hemodialysis, PD has advantages such as stable hemodynamics, lower risk of death (2) and better residual renal function preservation (3). In addition, studies have suggested that there is increased cognitive ability (4) and relatively low suicide rate (5) in patients on long-term PD treatment in comparison with patients treated with hemodialysis. Statistically, patients on PD treatment account for about 11% of the dialysis population worldwide, especially in developing countries (6). In the Unites States, China, and Thailand, the use of this therapy is increasing year on year (7). Nevertheless, PD treatment is still associated with significant adverse events. For example, long-term PD treatment can alter the structure and function of the peritoneum, leading to ultrafiltration failure and eventually withdrawal from PD (1). At present, risk factors in PD treatment include biocompatibility of the peritoneal dialysate, dialysis catheter factors and infection (8,9). However, due to the limitation of human experiments imposed by medical ethics, an in-depth understanding of PD is still needed. A suitable experimental model could help people better study the physiological and pathological changes in the peritoneum during PD treatment. Therefore, establishing an experimental model similar to human PD is of great significance for studying PD techniques, improving dialysis efficacy and prolonging the survival rate of patients.

2. Experimental animals

In recent years, scholars have studied and clarified the principles and characteristics of different *in vitro* experimental models using human tissues, and they have found that mesenchymal transformation of peritoneal mesothelial cells is closely related to peritoneal injury (10-12). *In vitro* models are usually obtained by culturing peritoneal mesothelial cells (13,14). This variety of model has advantages, such as relatively low cost, clear target and less confounding factors if a single cell type is used. Researchers can conduct an *in vitro* test of biocompatibility of the peritoneal dialysate through human peritoneal mesothelial cell culture (15).

In terms of *in vivo* animal models, researchers have attempted to use dogs, cats, rabbits, rats and mice to establish

PD models (16,17). However, due to the influence of many factors, such as cost and individual size of animals, different animals have specific advantages and disadvantages (Table I). From an economic cost perspective, rats and mice are cheaper and faster to breed, while rabbits, dogs, and cats are relatively expensive and less prone to reproduce. From the perspective of surgical operation possibility, rats have a strong peritoneal defense system, while rabbits are extremely prone to peritoneal infection, although their peritoneum is the most similar to the human peritoneum. In addition, PD requires catheter insertion in the abdominal cavity, and one should note that, catheter implantation is difficult in mice due to their small size. Therefore, rats are currently considered the most suitable animal PD model because of their low economic cost, the ease of performing a surgical operation on them and as they are a relatively stable model (16,18). However, in order to achieve better experimental results, different experimental animals should be selected according to different research purposes and actual conditions.

3. Classification of animal PD models

PD models can be applied for different research purposes, including for the study of peritoneal fibrosis (19,20), peritoneal sclerosis (21) and angiogenesis (22,23), and they can be divided into a uremic PD model and a non-uremic PD model. The uremic PD model refers to catheter implantation under the condition of uremia, which is achieved by nephrectomy or drug methods (24). If the creatinine and urea nitrogen levels are 2-3 times higher than those in normal rats, it is considered as successful establishment of an uremic animal model (25,26). After the model is successfully established, peritoneal dialysate can be infused directly or through a dialysis catheter that is already implanted. There are three main methods that are commonly used at present. The first method is direct intraperitoneal injection, which can be with or without anesthesia. However, this method can easily result in unintentional injection into the abdominal wall (as opposed to the intraperitoneal cavity) or even puncture of the blood vessels, bladder or intestines (27,28); additionally, repeated injections will increase the risk of infection (Fig. 1A). The second method is to establish open access characterized by a peritoneal catheter inserted subcutaneously into the peritoneal cavity of the animal then leading from the neck. The peritoneal dialysate can be injected directly into the catheter (Fig. 1Bb) and the catheter can be used as a fixed channel. During each exchange, a new sterile catheter is inserted for dialysate infusion. Upon completion, the sterile catheter is removed and the channel is sealed (Fig. 1Bb). Establishing open access does not require anesthesia, but the incidence of infection is high, and catheter failure frequently occurs due to hardening or adhesion of the omentum (27). The third method is to establish closed access. In this method, an incision is made under the skin of the neck, the catheter is permanently retained and connected to the peritoneal cavity through a subcutaneous tunnel from the neck, and the dialysate is retained in the abdominal cavity until it is completely absorbed (Fig. 1C). This method reduces the incidence of infection. However, catheter blockage is still a problem (29).

The non-uremic model is a PD model which is directly established in normal animals. Establishment methods can be further divided into the following two types: i) Intraperitoneal injection of the peritoneal dialysate alone; and ii) clinical simulation of an indwelling peritoneal dialysis catheter (29). Both methods have their advantages and disadvantages. Compared with catheter implantation, direct intraperitoneal injection is easy to perform and can avoid damage to the PD device caused by rats biting the catheter. However, repeated puncture will cause mechanical peritoneal damage and ultimately affect the experimental results (30). The catheter implantation model can be further divided into the large omentum intact and the large omentum resection models (27). The omentum is an organ with defensive function. In a normal rat PD model, keeping the large omentum intact during the PD process can reduce the incidence of infection, however, the incidence of catheter blockage is increased (31). Goh (32) proposed that peritoneal folding is a safe and effective technique to solve the issue of catheter occlusion.

4. Peritoneal function assessment

PD models are primarily used to study structural and functional changes in peritoneal tissues after long-term exposure to the peritoneal dialysate (33). Therefore, the success of an animal PD model is crucial for subsequent research. In addition, the success or failure of the model is assessed by evaluation of the functional changes in the peritoneum. At present, the commonly used method is the peritoneal equilibrium test. The main parameters include ultrafiltration volume, creatinine, urea nitrogen, and 24 h urine protein. The most commonly used parameters for evaluating peritoneal transport function are ultrafiltration volume and glucose transport volume, which are detected after the dialysate is left in the peritoneal cavity for four hours (34,35). Of note, is that uremia itself, following nephrectomy, also affects the peritoneal structure and permeability (25,36), which should receive comprehensive consideration in specific studies.

5. Choice of peritoneal dialysis catheter

Establishing smooth PD access is an essential step for successful PD treatment. PD catheter-related factors are the crux to establish this access. PD therapy is often withdrawn early due to catheter dysfunction related to catheter displacement, occlusion (32,37) and corrosion (38). Similar problems may also be encountered during the preparation of animal models. Moreover, the biomaterial present in the catheter can also affect the peritoneal structure (39). Consequently, the selection of higher quality PD catheters and appropriate implantation position can effectively reduce the occurrence of catheterization-related complications, such as exit site infection, poor peritoneal dialysate outflow, or leakage. Ross *et al* (40) found a significant reduction in tissue inflammatory cells occurred when coating the peritoneal dialysis catheter with a bioactive glass, which proved to have important research value and application prospects in preventing tunnel infection caused by the peritoneal catheter. In another experimental study of non-uremic peritoneal dialysis rats (41), improvement of the material and insertion method of the PD

Table I. Main advantages and disadvantages of animal experimental models commonly used in peritoneal dialysis (16-18).

Animal	Advantages	Disadvantages
Rat	Easy operation, low cost and easy reproduction	Short lifespan
Mouse	Low cost and easy reproduction	Small size and short lifespan
Rabbit	Peritoneum is similar to humans and long lifespan	High price and not easy to reproduce
Genetically modified mouse	Multiple possibilities of gene manipulation	Small size and short lifespan
Dog	Long lifespan and larger size	High cost and not easy to reproduce
Sheep	Long lifespan and larger size	High cost and not easy to reproduce

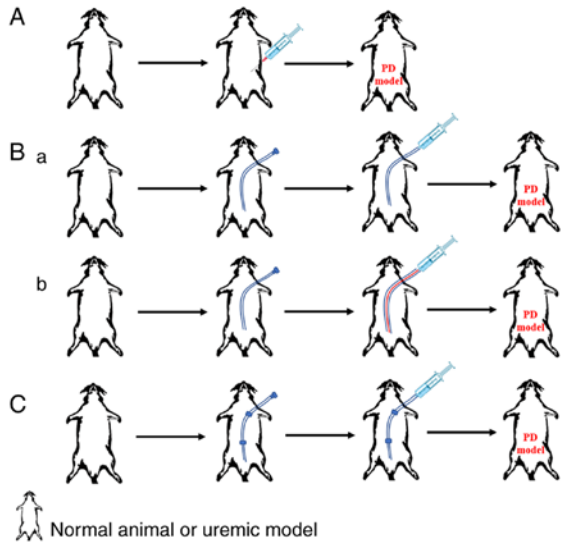

Figure 1. Classification of animal PD models. (A) Direct intraperitoneal injection. (Ba) To establish open access, peritoneal dialysate injected directly into the catheter. (Bb) To establish open access, a new sterile catheter is inserted for dialysate infusion during each exchange. (C) To establish closed access, the catheter is permanently retained and connected to the peritoneal cavity through a subcutaneous tunnel from the neck. PD, peritoneal dialysis.

catheter were described. The catheter was made of a silicone tube, and there was an iodophor cap on the external catheter branch that could easily be replaced. In the anesthetized rats, the back of the neck between ears and scapulae, as well as the right-side and left-side of the back under the arcus costarum were shaved. A longitudinal incision of 2 cm was made over the skin of the left or right back, at a distance of 1 cm below the arcus costarum and 1 cm from the lateral side to the spine. This type of catheter insertion rarely causes complications such as infection and catheter dysfunction. Additionally, it has advantages, such as convenient operation, cost and practicality, which make it worthy to use (41,42).

6. Potential complications in the preparation of a PD model

Selection of a non-uremic model or a uremic model. Non-uremic models can avoid complications caused by nephrectomy and the development of uremia in animals (41). Compared with non-uremic experimental models, uremic models can better simulate the clinical peritoneal dialysis process. However, the model preparation period is long, and hemorrhage, postoperative infection, and even death may occur during this preparation process (43). Therefore, different models should be selected according to different experimental purposes and actual conditions. Commonly used methods to induce uremia include nephrectomy and drug administration (44). Nephrectomy includes double nephrectomy (43), 5/6 nephrectomy and bilateral ureter ligation. Considering the technical aspects of the experiment, preparation cycle of the model and hemorrhage/infection risk during the preparation process, 5/6 nephrectomy is often the most suitable and is frequently used (25,29,45,46). Commonly used drug methods include adenine infusion (47,48) and adriamycin infusion (49). It is worth noting that different animal species have differences in model establishment. Specifically, 5/6 nephrectomy, adenine infusion or adriamycin infusion are usually used in rats, while bilateral nephrectomy and bilateral ureter ligation are typically used in rabbits (16,44).

Infection. Among the various complications of PD, the incidence of infection is relatively high and possible infections include peritonitis, subcutaneous tunnel infection and exit site infection. Subcutaneous tunnel infection and exit site infection are common causes of catheter extraction (50), while peritonitis is the most frequent and serious complication. As described by Tăranu *et al* (51), changes in peritoneal morphology usually occur 3-4 years after starting PD, and they progressively aggravate with passage of time on PD. When infection occurs near the PD catheter site, pus secretion, erythema, pain or swelling and other characteristics are often evident (52). Ordinary preventive measures against infection are administration of antibiotics, such as cefazolin and penicillin. In addition, injection of heparin on a regular basis was found to have a positive effect on prevention and treatment of catheter blockage (26,45). If infection occurs, antibiotics should be actively used once the infection is confirmed. PD should be restarted after the infection is treated. In severe cases, it may be necessary to arrange for catheter replacement or even PD termination (53).

Difference in peritoneal function between animals and humans. Knowledge of the differences between the animal peritoneum and human peritoneum in terms of morphology and functions is significant. The main feature of human peritoneum is that the peritoneal area is larger than the surface area of glomerular capillaries of both kidneys, which is conducive to peritoneal solute clearance (16,29). Differences in peritoneal morphology between humans and animals will inevitably lead to differences in physiological and pathological mechanisms

of peritoneal transport. Therefore, interspecific differences in peritoneal morphology should be considered when the results of animal experimental studies are extended to clinical research and application (54). Peritoneal surface area has an important effect on dialysis adequacy. Different animal models, with their different peritoneal surface area/body surface area ratios, will affect the dialysis efficiency (55). Another study found that the proportion of parietal peritoneal area in rats is larger than that in humans, that surface area of the peritoneum in lighter animals is also larger and that the surface area increases with aging in rats (56). Consequently, changes in the experimental results due to animal age and weight need to be fully considered in experimental research.

7. Conclusion

A successful PD model should simulate the clinical PD process and have characteristics including good reproducibility, feasibility and economic value. Additionally, it should also help in the process of deeply understanding the etiology and pathogenesis of PD-related diseases, providing guidance for clinical treatment and prolonging the duration where PD can be utilized as a dialysis method. There is currently no recognized standard model for studying PD, and there are great differences in the selection of animal models, administration routes, modeling methods and model evaluation methods. Moreover, due to the complexity and diversity of influencing factors in the PD process, it is often not possible to use a single experimental model for all aspects of the study. Therefore, future research is needed to establish a relatively standardized experimental PD model that is more in accordance with the clinical situation.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

BY, MMW and XT wrote and revised the manuscript. GA, LS and HTY reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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