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A Retrograde Implantation Approach for Peritoneal Dialysis Catheter Placement in Mice

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Abstract

Murine models are employed to probe various aspects of peritoneal dialysis (PD), such as peritoneal inflammation and fibrosis. These events drive peritoneal membrane failure in humans, which remains an area of intense investigation due to its profound clinical implications in managing patients with end-stage kidney disease (ESKD). Despite the clinical importance of PD and its related complications, current experimental murine models suffer from key technical challenges that compromise the models' performance. These include PD catheter migration and kinking and usually warrant earlier catheter removal. These limitations also drive the need for a greater number of animals to complete a study. Addressing these drawbacks, this study introduces technical improvements and surgical nuances to prevent commonly observed PD catheter complications in a murine model. Moreover, this modified model is validated by inducing peritoneal inflammation and fibrosis using lipopolysaccharide injections. In essence, this paper describes an improved method to create an experimental model of PD.

Introduction

End-stage renal disease burden

Chronic kidney disease (CKD) is a worldwide health problem[1]. Current estimates suggest that more than 850 million people worldwide have kidney disease. The prevalence of kidney disease almost doubles the number of people with diabetes (422 million) and is more than 20 times the prevalence of cancer (42 million) or HIV/AIDS (36.7 million) patients worldwide[2]. Approximately one in seven Americans have CKD, and two in 1,000 Americans have ESKD requiring a kidney transplant or dialysis support[3]. Considering the escalating burden of ESKD worldwide, optimizing dialysis technology is crucial[3].

Peritoneal dialysis

PD is a significantly underutilized modality for the treatment of ESKD in the United States. According to the United States Renal Data System (USRDS), the percentage of prevalent PD patients was only 11% in 2020[4,5]. PD confers several advantages over in-center hemodialysis (HD), including a better quality of life, fewer clinic visits, and a decrease in Medicare expenditures[6,7]. Additionally, PD is a home-based therapy and is associated with a much lower risk of severe infections such as bacteremia and endocarditis that are often related to hemodialysis catheters. Furthermore, PD can be initiated rapidly with an urgent start protocol, decreasing the need for dialysis initiation with indwelling vascular catheters[8]. PD is considered the preferred method of dialysis in the pediatric ESKD population[9].

Peritoneal impairment induced by peritoneal dialysis

PD entails introducing PD fluid (dialysate) into the peritoneum, which results in inflammation and remodeling of the peritoneal membrane over time. Peritoneal inflammation triggers fibrosis, culminating in the potential loss of ultrafiltration capabilities of the membrane over time. Preservation of the peritoneal membrane is a significant challenge in PD, and further research is critically important to ensure that best clinical practices are available to practitioners. There are well-established murine models to help further the understanding of pathophysiological mechanisms of peritoneal infection and inflammation, solute, water transport kinetics, and membrane failure; still, technical issues with the catheter often limit these models[10].

Analyzing the peritoneal membrane changes

In ESKD patients, dialysate is traditionally introduced in the peritoneal cavity through a Tenkhoff catheter with a deep and superficial cuff. The patients can potentially experience catheter-related complications, including catheter migration, infusion pain, and poor drainage of the dialysate[11,12,13]. Two major types of peritoneal catheters have been introduced for humans, coiled or straight, to minimize these complications[12]. Several modifications, including an extra cuff to the conventional two-cuffed catheters, have been added to the original catheters to prolong PD catheter survival[11]. The insertion technique varies according to several factors by preventing catheter migration to be added after survival, including the availability of the resources and the level of expertise[14].

In contrast, the murine models of peritoneal dialysis have fundamental differences in techniques and purpose compared to human peritoneal catheters. For example, peritoneal catheters in murine models are used primarily to study membrane alterations and are less intended for bidirectional drainage functions. The current technique suffers from potential port dislodgement and catheter migration due to the handling of the animals. In the conventional murine models, the access ports were not fixed to the skin. This aspect created an unstable access port, which in awake animals might get dislodged, resulting in catheter migration. Given the importance of murine models in peritoneal membrane research, it is imperative to create effective surgical techniques to generate reliable models. Therefore, we set out to optimize the conventional model of PD catheter placement. It is important to note that the catheter itself causes histopathologic alterations in the peritoneal membrane, and, thus, any conclusions regarding the effect of PD solutions in animal studies must be interpreted in the context of the PD catheter as a foreign body[15,16,17].

Peritoneal membrane histopathology

PD failure is mainly related to fibrosis and excess angiogenesis resulting in the loss of an osmolar concentration

gradient. In addition, the peritoneal membrane filtration capacity might be affected by peritonitis. In addition, infectious peritonitis is a well-established cause for change in the dialysis modality from peritoneal dialysis to hemodialysis.[18].

Protocol

For this study, eight female C57BL/6J mice, 8-12 weeks in age, and an average weight of 20 g were used. The mice were housed under standard conditions and were fed with chow and water *ad libitum*. This study was performed with the approval of the Institutional Animal Care and Use Committee (IACUC), Boston University Medical Center (AN-1549). The procedures described here were performed under sterile conditions.

1. Anesthetize the mouse in an Isoflurane chamber, and inject the analgesic subcutaneously

1. Hold the animal from the base of the tail. Keep the animal on the dorsum surface of the non-dominant hand.
2. Transfer the animal to the continuous anesthetic induction chamber filled with 3%-4% isoflurane. Confirm adequate general anesthesia by the absence of toe-pinch reflex in the right and left hind limbs. Keep the maintenance of the general anesthesia with Isoflurane 1%-3%.
3. Apply vet ointment on both eyes.
4. Administer a subcutaneous injection of Buprenorphine.
    1. Dissolve the stock of Buprenorphine at a concentration of 0.3 mg/mL in sodium chloride (NaCl) 0.9% to achieve the final concentration of 0.03 mg/mL.
    2. Inject a dosage of 0.05-0.1 mg/kg of 0.03 mg/mL Buprenorphine, together with 500 µL of sterile NaCl 0.9%, 20 min before surgery in a 20 g mouse (2 µg or 66 µL of 0.03 mg/mL Buprenorphine per mouse).

2. Skin preparation

1. Place the fully anesthetized mouse in a left lateral position, exposing its right flank to the heating blanket. Shave the right side of the abdomen, just close to the midline to the paraspinal area, and down to the animal's tail. Disinfect the shaved area with chlorhexidine tincture 0.5% twice.

    NOTE: Frequently check the temperature of the heating blanket during the procedure to ensure that the temperature does not fall.

3. Measure the catheter length and mark the insertion point within the abdomen and the tube tract over the prepared skin

1. Assign the access port pocket 1 cm above the animal's tail. Hold the installation segment with the non-dominant index and thumb finger over the assigned area near the tail.
2. Place the catheter above the skin and estimate the place for the catheter's tube insertion within the abdominal cavity. Mark the assigned place for tube insertion, respecting the minimal bending of the tube near the anterior midline.

    NOTE: All the procedures must be performed with sterile gloves, and the catheter should be kept sterile during the measurement. Surgical tools must be autoclaved at 121 °C before use. Refer to **Supplemental Figure S1** for the instruments required for the procedure.

4. Customize the peritoneal catheter reservoir section

1. Punch a side hole over the frame of the reservoir section with the mouse ear tagger (**Figure 1** and **Figure 2**).

5. Place the instillation port

1. Make a horizontal 1 cm wide skin incision 1 cm above the tail. Bluntly dissect the subcutaneous plane from the underlying muscular layer to make a pouch for the catheter placement to ensure the instillation port resides in the ideal port pocket freely.
2. Keep the iris scissors' tip toward the midline to make an oblique tunnel for the tube placement (**Figure 3A**).
3. Pass the 3.0 suture from the customized side hole. Fix the access port to the muscular bed by tightening the passed suture, keeping the tubing course cephalad.

6. Make the catheter tip insertion site incision

1. Make a 1 cm incision over the formerly marked area near the midline. Confirm the well-developed tract by passing scissors through the tract.
2. Pick the catheter tip gently with forceps to place the catheter in a retrograde course.
   NOTE: Avoid pinching the side holes of the tube.
3. Pass the catheter tube through the prepared tract (**Figure 3B**). Make a 1 cm incision over the muscular layer close to the right midline.

7. Confirm the functioning of the catheter

1. Before closing all the incisions, make sure the placed catheter is functional. Check the function with a 1 mL syringe attached to the specific Huber needle for the port.
2. Inject 200 µL of normal saline into the instillation port. Look for a smooth flow with a zero tolerance for resistance.
3. Flush the port and catheter with 10% heparin to maintain patency.

8. Close the skin incisions

1. Close the skin incisions around the port reservoir (**Figure 3C**) with 3-0 absorbable sutures.

9. Fix the catheter tip inside the abdominal cavity

1. Place a loose purse-string suture with 4-0 round absorbable suture around the incised abdominal wall muscle. Pass the proximal felt of the catheter inside the incision.
2. Tighten the prepared purse-string suture around the tube while keeping the second felt outside the purse string, over the muscular layer (**Figure 3D**), and close the skin with 3-0 absorbable sutures (**Figure 2**).

10. Monitor the animals postoperatively and daily, administer postoperative analgesia and fluids, and maintain daily postoperative records for a minimum of 7 days and until complete recovery

1. Keep the catheter functional with a daily injection of 200 µL of normal saline through the catheter.

11. Fluid injections

1. Confirm the uneventful postprocedural process by carefully inspecting the skin incision.
2. Prepare LPS 2 mg/kg body weight for intraperitoneal injections (i.p.) by diluting 40 µg of the LPS with sterile phosphate-buffered saline (PBS) to the working

concentration of 0.2 µg/µL (in essence, 10 µL for 2 µg/g body weight and 200 µL of LPS for 20 g mice).

3. Start the injections in the second week following the catheter implantation.
    1. Hold the animal gently with the non-dominant hand and restrain the instillation port while moving the index and thumb fingers in the cephalad direction.
    2. Disinfect the skin overlying the reservoir with 70% isopropyl alcohol. Use the syringe attached to the Huber needle to inject the LPS.
        1. After entering the port with the Huber needle, inject 100 µL of normal saline into the port to confirm the patent course.
        2. Inject the prepared 200 µL of LPS, followed by the 100 µL of normal saline for tube irrigation, and make sure there is no resistance.

12. Anesthetize the mice before harvesting the peritoneum and collect the peritoneal fluid

1. Following 7 days of LPS injections and 2 weeks of catheter implantation, plan for the peritoneal biopsy.
2. Plan for general anesthesia.
    1. Anesthetize the mouse in an isoflurane chamber and inject the analgesic subcutaneously.
    2. Hold the animal from the base of the tail, and keep the animal on the dorsum surface of the hand.
    3. Transfer the animal to the continuous anesthetic induction chamber filled with 3%-4% isoflurane. Confirm adequate general anesthesia by the absence of toe-pinch reflex in the right and left hind limbs. Keep the maintenance of the general anesthesia with isoflurane 1%-3%.

13. Peritoneal biopsy

1. Place the animal on the heated blanket in the supine position. Make a midline skin incision from the sub-xiphoid to the bladder.
2. Perfuse the subfascial plane with cold PBS (**Figure 3E**).
3. Make sure the plane is completely dissected without disturbing the integrity of the peritoneum. Start dissecting the peritoneum from the lateral peritoneal reflection at the left lower quadrant, starting from the hilum to the left flank, and bladder in the lower aspect to keep samples consistent between animals (**Figure 3F**).
4. Following the peritoneal harvest, euthanize the animal by cervical dislocation.

Representative Results

All the implanted catheters were functional till the end of the study, and catheter dislodgement or kinking did not complicate any of the implanted catheters. The current, modified technique was further validated with a peritonitis-induced model using LPS. The control mice received 200 µL of daily normal saline injections, while the experimental mice were injected with 200 µL of LPS, as discussed in protocol step 11, for a total of 7 days following catheter implantation.

The peritoneal membrane was evaluated for histopathological characteristics by hematoxylin and eosin (H&E) and Masson Trichrome staining. Analysis of the H&E-stained sections showed a substantial increase in the extracellular matrix (ECM) in the sub-peritoneal space (**Figure 4A**, marked with an asterisk), which was measured using ImageJ. The average + SD of ECM in the sub-peritoneal space of the control mice

was 87.10 + 24.66 µm and doubled in LPS-exposed mice (148.9 + 60.85 µm, P = 0.008) (**Figure 4B**).

The trichrome stain detects fibrosis (blue stain in **Figure 5** and **Figure 6**), which was estimated as intensity density normalized to the surface area (µm). Intensity density integrates the number of pixels and their intensity in a region of interest and is a validated method for quantitative histological features of interest[19,20].

Next, we posited that LPS-induced inflammation may result in altered vascularity and widening of the sub-peritoneal space. CD31 was used as a marker for endothelial cells (**Figure 7**) and quantitated as integrated density in randomly selected high-power field (HPF) images in each mouse in both groups (**Figure 8B,C**). LPS-induced mice showed a three-fold increase in sub-peritoneal fibrosis (**Figure 8A**, P = 0.015). All these alterations in the peritoneal membrane are consistent with those observed in patients exposed to long-term dialysates[21]. The results showed an ~8-9-fold increase in the vascularity (P = 0.0168) (**Figure 7** and **Figure 8B**) and a ~2-fold increase in the sub-peritoneal space marked as SP (P = 0.008) (**Figure 7** and **Figure 8C**). These results are consistent with the neovascularization observed in patients on PD after long-term exposure to the peritoneal membrane to the dialysate[18,22,23].

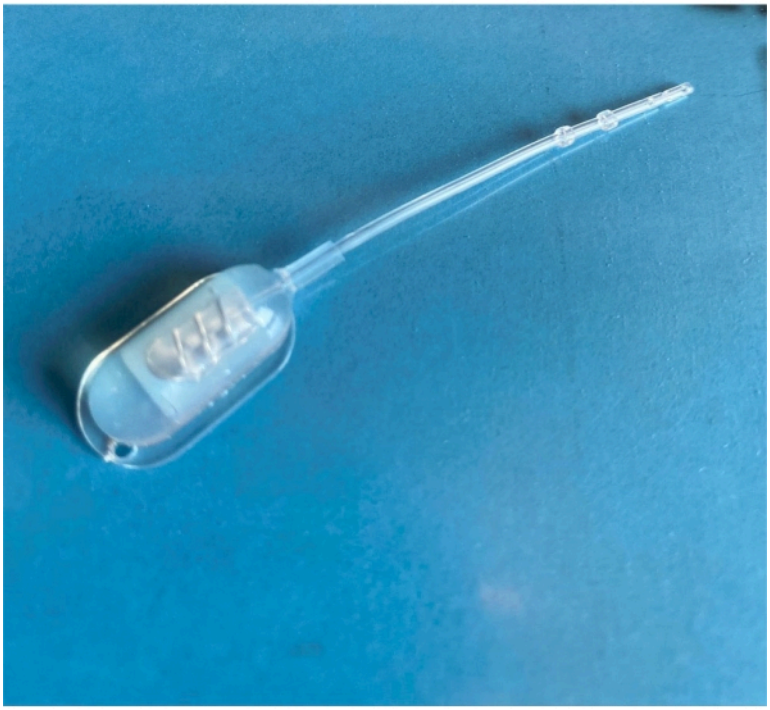

Figure 1: PD catheter and the customized side hole. Abbreviation: PD = peritoneal dialysis. Please click here to view a larger version of this figure.

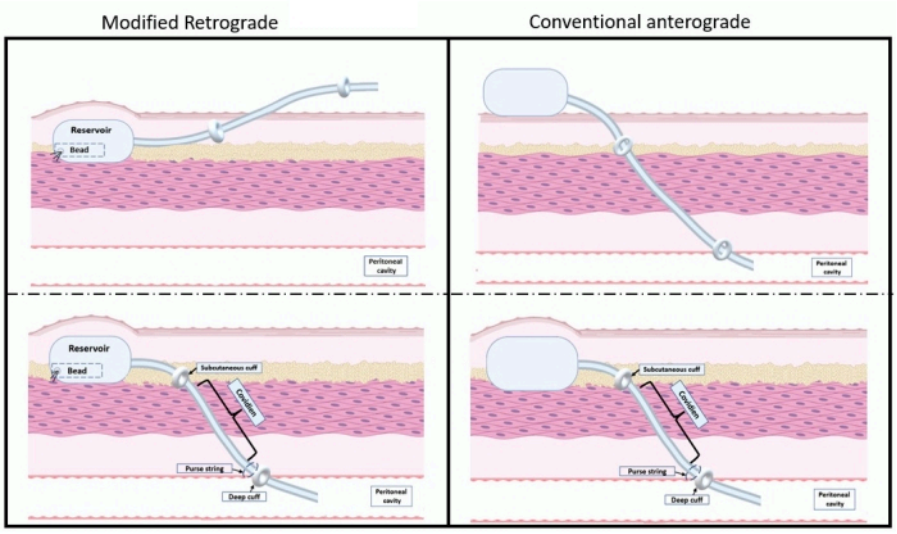

Figure 2: Conventional versus modified methods. Conventional antegrade method of PD catheter placement (right) starts with securing the inner ring in the parietal peritoneum, while in this modified retrograde method (left), the procedure starts with suturing the customized access port over the muscular bed on the dorsum of the mice. Please click here to view a larger version of this figure.

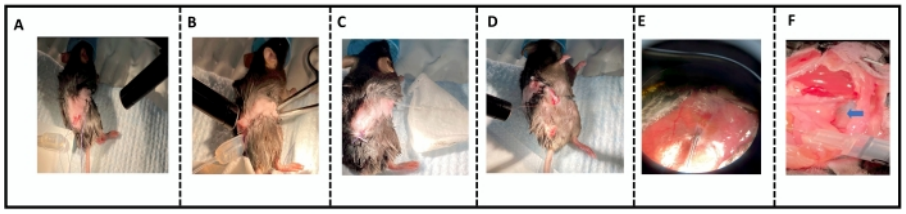

Figure 3: Inserting the peritoneal catheter. (**A**) Pass the 3.0 suture from the customized side hole and suture the muscular bed to the side hole, keeping the tubing course cephalad. (**B**) Make the tunnel of the PD tube with meticulous dissection of the muscular layer from the overlying skin and pass the tube in a retrograde manner. (**C**) Close the skin incisions around the port reservoir. (**D**) Tighten the prepared purse-string suture around the tube while keeping the second felt outside the purse string, over the muscular layer. (**E**) Irrigate the peritoneal cavity with 2 mL of cold PBS while keeping the needle bevel up. (**F**) Start dissecting the peritoneum from the lateral peritoneal reflection at the left lower quadrant (blue arrow). Abbreviations: PD = peritoneal dialysis; PBS = phosphate-buffered saline. Please click here to view a larger version of this figure.

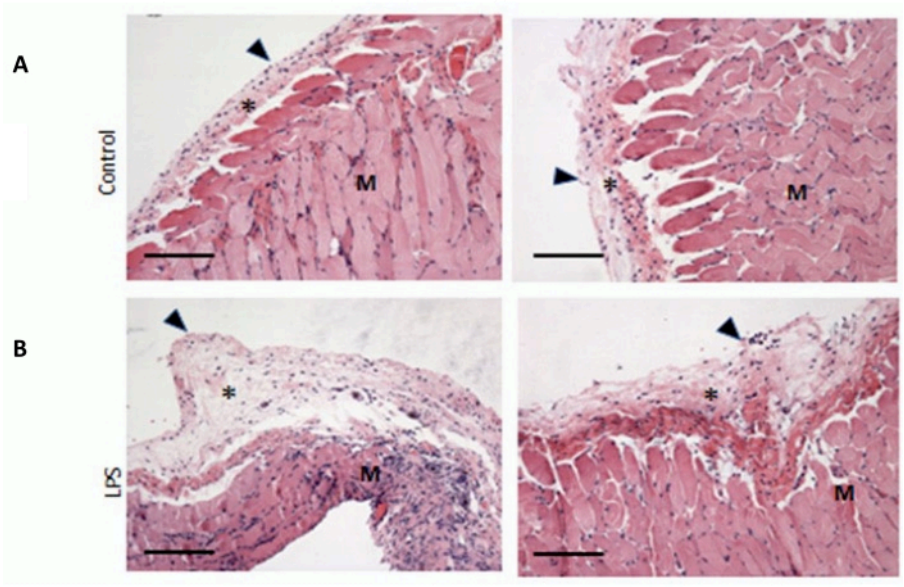

Figure 4: H&E staining. Representative images (100x) of peritoneal membranes of two individual C57BL6 mice exposed to LPS in the experimental group as indicated (N = 4/group). Black arrowhead points to the peritoneum, and an asterisk depicts the sub-peritoneal space. Scale bars = 100 µm. Abbreviations: H&E = hematoxylin and eosin; M = muscle; LPS = lipopolysaccharide. Please click here to view a larger version of this figure.

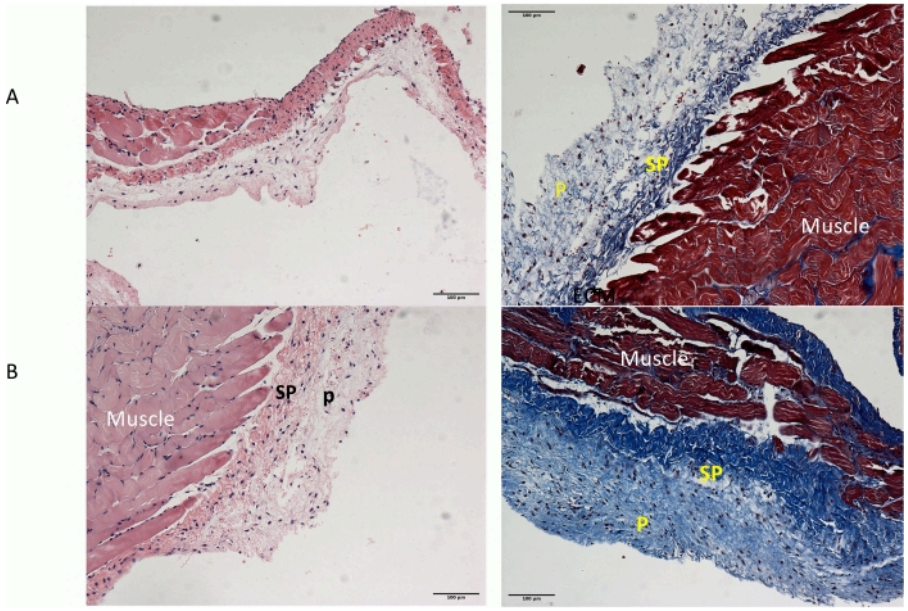

Figure 5: H&E and Masson Trichrome staining. Representative images (100x) of peritoneal membranes of two C57BL6 mice, one in control group (**A**) and one exposed to LPS in the experimental group (**B**). Scale bars = 100 µm. Abbreviations: SP = sub-peritoneal space; P = peritoneal space; M = Muscle; H&E = hematoxylin and eosin; LPS = lipopolysaccharide.

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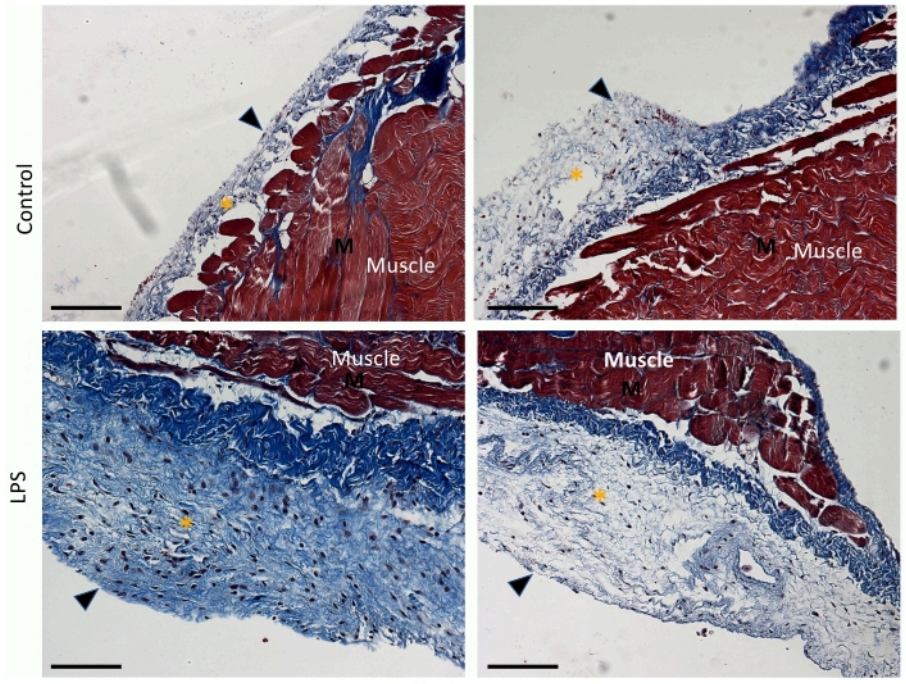

Figure 6: Masson Trichrome staining. Representative images (100x) of peritoneal membranes of two C57BL6 mice, one exposed to LPS and the other a saline-injected control. Black arrowhead points to the peritoneum, and orange asterisk depicts the sub-peritoneal space, N = 4/group. Scale bars = 100 µm. Abbreviations: M = Muscle; LPS = lipopolysaccharide.

Please click here to view a larger version of this figure.

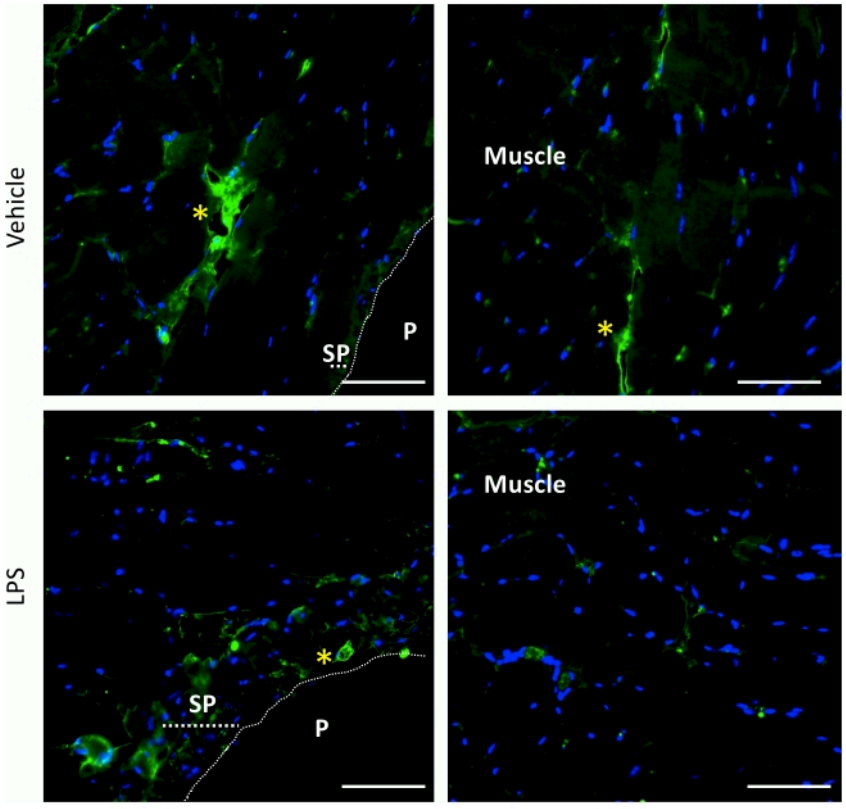

Figure 7: Altered vascularity in the sub-peritoneal space in the context of inflammation. Paraffin-embedded sections were stained with CD31 and DAPI. Random images obtained at 400x magnification are shown. Scale bars = 100 µm. Abbreviations: SP= sub-peritoneal space; P = peritoneal space; white asterisk = sub-peritoneal vessel; DAPI = 4',6-diamidino-2-phenylindole. Please click here to view a larger version of this figure.

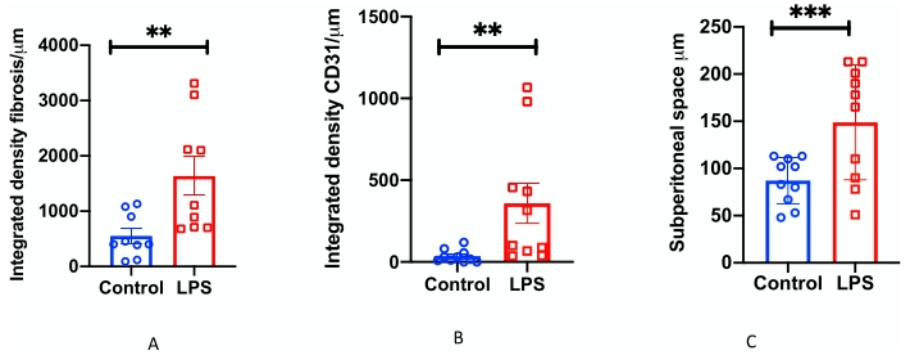

Figure 8: LPS exposure enhanced the neovascularization, fibrosis in the peritoneum, and expansion of sub-peritoneal space. (**A**) Integrated density of fibrosis. (**B**) Integrated density of CD31. (**C**) Sub-peritoneal space was measured. Student's *t*-test was performed for all the measures. Black asterisks depict the level of significance. Error bars = SEM. Abbreviation: LPS = lipopolysaccharide. Please click here to view a larger version of this figure.

Supplemental Figure S1: Surgical instruments required for performing the procedure. 1. Ear Tagger, 2. Minute mouse port, 3. Huber point needle, 4. Delayed-absorbable suture, 5. Right-angle clamp, 6. Straight tip forceps, 7. Curved-tip forceps, 8. Iris Scissor. Please click here to download this File.

Discussion

Three murine models of PD are described. This includes a blind puncture of the peritoneal surface, an open-permanent system, and a closed system[10]. The blind puncture of the peritoneal surface involves direct peritoneal access similar to intraperitoneal injections but does not allow drainage of dialysate. Being a blinded procedure, this method can injure the abdominal visceral organs. The open-permanent system model keeps the dialysis catheter and instillation port outside the body. However, this technique in mice is associated with complications, such as disconnected bags due to the movement of animals, infection, and inability to perform long-term experiments. Closed-system peritoneal catheters were introduced in 2009. In this system, both the access port and the tube are implanted in the animals' bodies. Direct percutaneous fluid instillation becomes feasible. In humans, the peritoneal dialysate bags are placed external to the body, but this is not possible in mice due to their mobility. In addition, there is often mechanical obstruction of the catheter-related to the side holes clogging and the tube bending[20]. The reservoir in a closed system is mobile and can flip, and this event can kink the reservoir-tube junction.

Several approaches have been applied to overcome the above limitations of closed PD systems, including omentectomy and heparin infusion to prevent PD catheter clogging. Although these solutions might be useful in the short-term studies, the challenges to rescuing the catheter for longer experiments in murine models persist. Moreover, the omentum in mice is small, unlike in humans, explaining the lack of success with omentectomy to rescue the peritoneal catheter performance in mice[24,25].

In this study, two critical steps were applied to the closed PD catheter system to improve the limitations of the current techniques. These included (a) punching a side hole in the catheter and (b) a retrograde tube passing through a prefabricated tunnel. (**Figure 3B**) Punching a side hole in the instillation port assisted in fixing the catheter securely to the muscular bed and provided mobility during the injections. While addressing the above limitations, this modification reduced the tugging of the tube and straining of the skin of mice.

Traditionally, the PD catheter tip goes into the peritoneal cavity first at the time of implantation (antegrade implantation). We introduced a retrograde implantation approach where the instillation port was fixed on the skin first, and then the catheter was placed in the peritoneal cavity. Since the catheter implantation followed the reservoir placement, it is considered retrograde catheter implantation. This method of implantation resulted in a straight course of the tube and abrogated tube coiling.

A potential limitation of the technique can be the straining of mice skin from the suture. The significance of the modified technique is underscored by the fact that these proposed modifications prevent catheter migration and tugging of the tube. It allows precise instillation of the PD fluid while the mouse is awake. Reduction in the above problems permits long-term experiments and avoids failures, thus precluding the use of a large number of mice. In addition to the application in PD research, these modifications can be leveraged in other contexts such as ovarian cancer models, peritoneal carcinomatosis, or chronic peritonitis to precisely deliver experimental agents.

LPS injection was selected for validation of this modified implantation method. The findings were consistent with those observed in response to icodextrin and glucose-based peritoneal dialysis fluid[26]. Furthermore, the use of LPS is clinically relevant as PD peritonitis in humans can be from gram-negative bacteria and is frequently observed in the setting of diverticulitis or viscus perforation. Gram-negative bacteria secrete LPS contributing to peritonitis and is an accepted experimental model of peritonitis[26,27]. The pathologic features of PD failure in humans include peritoneal fibrosis and an increase in the sub-peritoneal microvasculature, which results in the loss of peritoneal solute gradient in PD patients[27,28,29]. These features were recapitulated in the LPS-induced peritonitis model. Future studies will further examine this technique in models wherein the peritoneal dialysis fluid will be applied for at least 1 month in mice to induce peritoneal fibrosis. This long-term study will also enable the follow-up of complications, including coiling of the PD catheters.

In conclusion, the conventional closed system peritoneal catheter implantation in a murine model was modified in the current study. The current modifications might pave the way for the generation of robust and reliable murine models to investigate the long-term consequences of peritoneal membrane failure in human ESKD patients.

Disclosures

The authors have no conflicts of interest to disclose.

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