الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Post-Market Clinical Evaluation for the Safety of Peritoneal Dialysis

Background

The safety of peritoneal dialysis was evaluated for the potential infectious complications, mainly the peritonitis, in reference to some medical devices reports at the National Center of Medical Devices Reporting (NCMDR). Further analyses at the US FDA database revealed the availability of 2601 reports, through which 52 reports caused fatal incidents and 182 were reported to result in serious injuries. In addition, data provided by the Saudi Center for Organ Transplantation illustrate a mortality rate of about 6% of the PD population in Saudi Arabia, in 2019 [8].

The aim of this study is to evaluate the safety of peritoneal dialysis in general, and to test, in particular, whether the current local rate of peritonitis is within the acceptable rate, as indicated by reliable global societies, or otherwise, to recommend certain actions to ensure the safety of the device.

Clinical burden

Peritoneal dialysis refers to the treatment used to compensate some lost kidney functions, which use the lining of the abdominal cavity, peritoneum, to serve as a filter for the dialysis process to be completed inside the body. Before starting the peritoneal dialysis, a catheter must be implanted permanently into the belly or the chest to allow the flow of a solution called dialysate in and out of the abdominal cavity. [9] The dialysate is a solution that contains electrolytes to help maintain blood composition, an osmotic agent and a pH buffer. [10] Long-term catheters are usually made of silicon with a strip of radiopaque to be visualized on x-ray. The catheter is divided into three sections: an intraperitoneal section, a subcutaneous section and an external section to be connected to the dialysis system. Two cuffs are implanted for catheter stabilization, movement limitation, leaks prevention, and microorganisms' entry control, as illustrated in figure 1. [11]

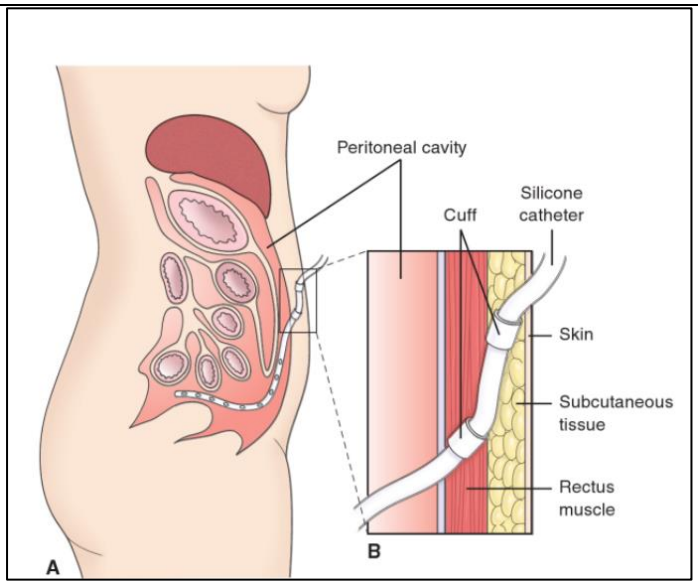

FIGURE 1. (A) AN IMPLANTED PERITONEAL CATHETER. (B) A CLOSE-UP SHOWING THE STABILIZING CUFFS. [11]

The process of filling and draining the dialysate is called an exchange. Patients do exchanges in accordance to two types of peritoneal dialysis, which are Continuous Ambulatory Peritoneal Dialysis (CAPD), or Automated Peritoneal Dialysis (APD), as illustrated in figure 2. These types are almost similar, except for the exchanges schedule, which is done automatically with APD [7]. In CAPD, patients usually are prescribed to do four exchanges a day, with each exchange the dialysate will sit in the abdomen for a dwell time while maintaining their daily activities. On the other hand, APD is usually done at night while the patient is asleep, using a machine called cycler.

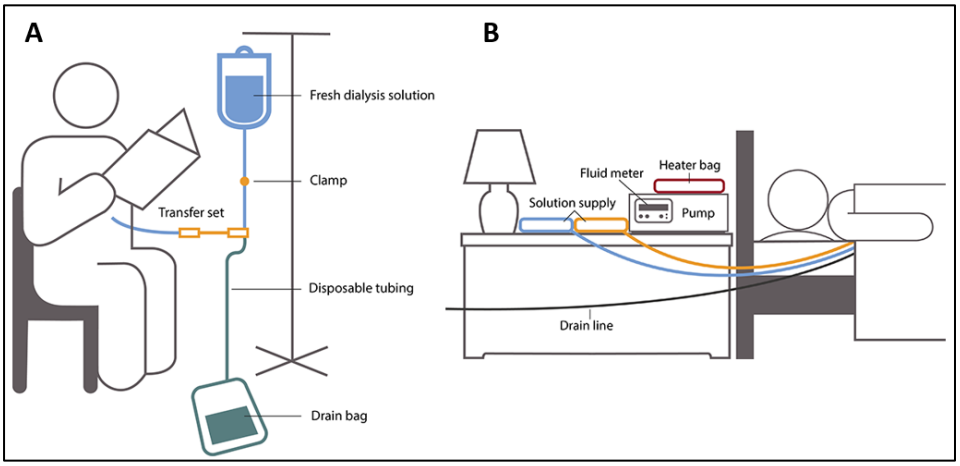

FIGURE 2: MODE OF OPERATION OF PERITONEAL DIALYSIS. A: CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD), B: AUTOMATED PERITONEAL DIALYSIS (APD) [7]

Risks and complications

Given that peritoneal dialysis is a home-use system, the most common complication is infections. Peritoneal dialysis is potentially associate with two types of infections, which are catheter related infections and peritonitis. Peritonitis is the inflammation of the peritoneum, which is reported to contribute to death in 16% of PD patients [1]. Catheter related infections, on the other hand, are divided into tunnel and exit-site infections, both of them are susceptible to lead to serious consequences including peritonitis. The International Society of Peritoneal Dialysis (ISPD) recommended monitoring PD programs to maintain an overall peritonitis rate that does not exceed 0.5 episodes per patient-year [13].

Peritoneum inflammation is usually caused by contamination, in which microorganisms find their ways inside the abdominal cavity through the catheter tube. Peritonitis is mostly caused by the touch contamination [1], beside other sources of contaminations as indicated in table 1.

Source of Peritonitis	%
Touch Contamination	41%
Catheter related	23%
Enteric injury	11%
Perioperative	6%
Diarrhea/UTI	4%
Sepsis	1%
Unknown	14%

TABLE 1. CAUSES OF PERITONITIS AND THEIR POSSIBILITIES.

Evaluation Outcomes

Part 1: Clinical Paper Review for the Safety of Peritoneal Dialysis

1.1 Search criteria

The search criteria followed some measures to define the research question, relative databases, inclusion criteria, and quality measures. A total of 86 articles were acquired for the period of 2012-2020. The screening process resulted in obtaining 22 articles to be included in the clinical evaluation, as shown in figure 3.

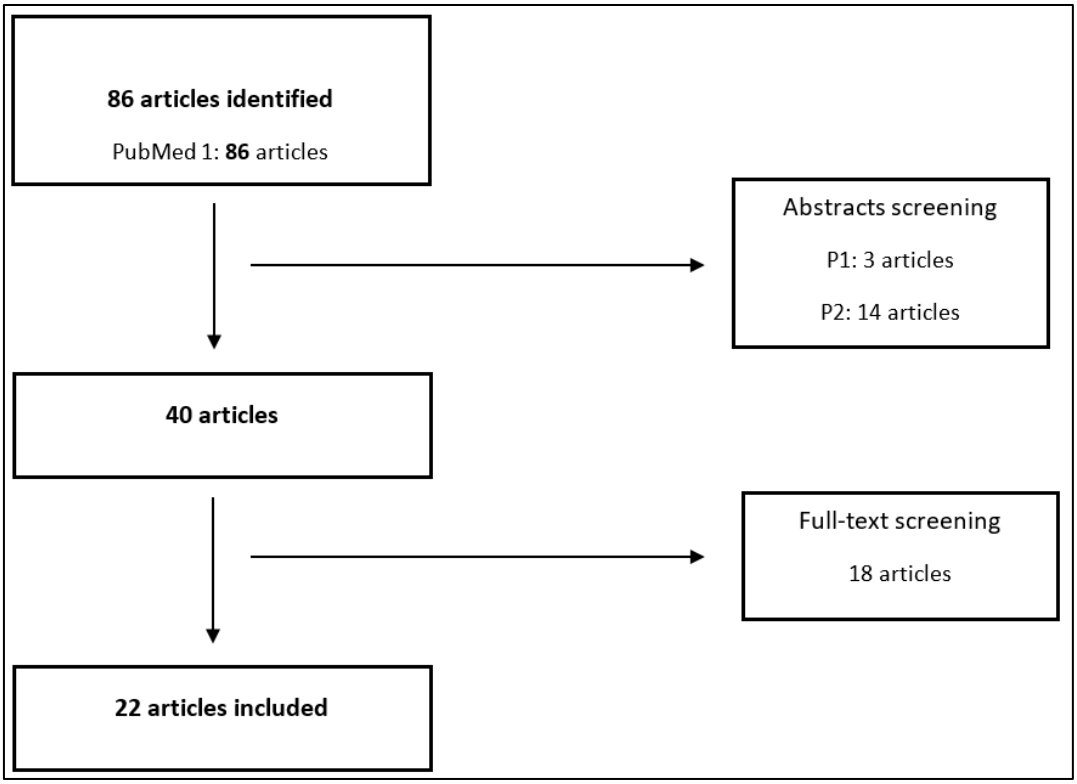

FIGURE 3. SCHEMATIC REPRESENTATION OF THE SEARCH FINDINGS ON EVALUATING THE SAFETY OF PD IN REGARDS TO THE PERITONITIS RATE.

1.2 Summary of the literature findings:

The ultimate aim of the review was to discover the range of the peritonitis rate as revealed by the published literature. This is an issue of interest in Saudi Arabia, since it triggered a safety concern that threatens patients' lives. Table 6 illustrates the data obtained from 22 articles, which reported peritonitis rates ranging from 0.13 to 0.87 episode per patient-year with an average of 0.3 episode per patient-year.

TABLE 2. SUMMARY OF THE PAPER REVIEW FINDINGS THAT REVEAL THE PERITONITIS RATE IN DIFFERENT STUDIES.

Reference	Study design	Number of patients	Follow-up (months)	Peritonitis rate (episode-patient-year)
Balzer, S. et al. [16]	Prospective	160	Max 120	0.24 ± 0.11
Chen, H. et al. [17]	Retrospective	514	Median of 21.3	0.18
Luo, Y. et al. [18]	RCT	73	12	0.408
Hu, S. et al. [19]	Retrospective	278	Median of 33	0.27
Hsu, C. et al. [20]	Prospective	169	60	0.29
Jegatheesan, D. et al. [21]	Retrospective	8343	Median of 16	0.50
Davidson, B. et al. [22]	Retrospective	199	Average of 17	0.87
Al Wakeel, J. et al. [23]	Retrospective	111	Average of 23.35	0.34
Nataatmadja, M. et al. [24]	RCT	177	24	0.31
Yan, H. et al. [25]	RCT	139	24	0.13 and 0.20
El-Reshaid, W. et al. [26]	Retrospective	341	120	0.26 (CAPD) 0.37 (APD)
Neu, A. et al. [27]	Retrospective	644	36	0.42
Wu, H. et al. [28]	Retrospective	1,690	12	0.158
Ong, L. et al. [29]	Prospective	1,603	12	0.273
Pai, M. et al. [30]	Prospective	69	30.5 ± 24.9	0.13
Fan, X. et al. [31]	Retrospective	1117	26.1	0.2
Prasad, N. et al. [32]	Prospective	328	20.0 ± 14.3	0.46
Sanabria, M. et al. [33]	Retrospective	345	Average of 15.6	0.305
Hsieh, Y. et al. [34]	Retrospective	391	35.5 ± 27.6	0.196
Chern, Y. et al. [35]	Retrospective	404	37.9 ± 27.3	0.226
Su, C. et al. [36]	Prospective	158	24	0.158
Xu, Rong et al. [37]	Prospective	313	44.5	0.216

Part 2: Clinical Experience Review for the Safety of Peritoneal Dialysis

The international society for peritoneal dialysis (ISPD) is a society built to promote quality practice, and achieve optimal outcomes of peritoneal dialysis through enhanced advocacy, research, and education, in order to improve the health and well-being of people living with end-stage kidney disease or suffering from acute kidney injury. In 2016, the ISPD published a guideline to clarify the correct practices of the treatment and prevention of peritonitis. This section aims to state the ISPD recommendations regarding the peritonitis rate in PD units and the best practices to prevent peritonitis from occurring [13], and to reflect the Saudi users' opinion in the topic.

2.1 ISPD peritonitis-related recommendations:

- All PD units should monitor the peritonitis incidence within their facility on regular basis. Episodes of peritonitis should be counted starting from the beginning of PD training, whereas all relapsing episodes should be counted as one. The monitored parameters should include the following: overall peritonitis rate, peritonitis rates of specific organisms, peritonitis-free patients' percentage, and the antimicrobial susceptibilities of the infecting organisms.
- The overall peritonitis rate is recommended to be reported as episode per patient-year and should not exceed 0.5 episodes per patient-year at risk.

2.2 Saudi Users' Experience Review

In order to reflect the local situation of PD in Saudi Arabia, local experts were consulted to give opinion regarding the current situation of the safety of PD. The advisory panel were represented by nephrologists from different healthcare facilities in Saudi Arabia.

The consulted experts highlighted that peritonitis and infectious complications have been an issue since the inception of PD modalities as a kidney failure treatment. However, wrong practices could be the cause of infections rather than the PD modality itself. Therefore, manufacturers should focus on the internal training at the hospitals, in addition to the home visits. In addition, it is also highlighted that the currently available data related to PD

complications at the national level are known through the voluntary efforts of some organizations, but there is no reliable source to have clear and precise rates of such complications. Thus, manufacturers shall monitor the overall peritonitis rate among PD patients by keeping records of every peritonitis case.

SFDA actions

In order to maintain the PD patient safety, and to reduce the potential risk of peritonitis, SFDA has established several meetings with the PD-related manufacturers in the Saudi market, and end-up with some actions that should be fulfilled, which are:

- Manufacturers of PD shall provide a plan to collect clinical data from the Saudi healthcare facilities, in regards to monitoring the peritonitis cases and rates.
- Manufacturers of PD shall implement the plan to monitor the peritonitis cases and rates as part of their post-market surveillance plan, and to submit to SFDA a monthly report that shows maintaining the peritonitis rate within the accepted international standards.
- Manufacturers of PD shall report to SFDA all PD-related incidents whenever received from PD users.

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For inquiries related to this study, you may reach us through this email: cia.md@sfda.gov.sa

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