CLINICAL RESEARCH IN A MODERN CHINESE PERITONEAL DIALYSIS CENTER

Jie Dong and Ming-hui Zhao

Renal Division, Department of Medicine, Peking University First Hospital; Institute of Nephrology, Peking University; Key Laboratory of Renal Disease, Ministry of Health of China; and Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, PR China

A prerequisite for enhancing the quality of peritoneal dialysis is the continuous review and analysis of clinical data from routine clinical care and research. Here, we describe our strategy (Peking University First Hospital, Beijing, China) to achieve that objective.

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The Renal Division of Peking University First Hospital, also called the Institute of Nephrology of Peking University (INPU), was the first renal unit in China, established nearly 60 years ago by Professor Shu-xian Wang (now deceased), the founder of modern nephrology in China. Since the early 1980s, this division, under the leadership of Professor Hai-yan Wang, has been one of the top referral diagnostic, therapeutic, and clinical research centers in China. Currently, INPU has gained an international reputation for work in various areas of clinical research, such as epidemiology (1), immunologic mechanisms (2,3), the genetic background of glomerular diseases (4,5), and peritoneal dialysis (PD) (6,7).

The PD center at INPU is now one of the largest PD units in China, with a multidisciplinary PD team that includes 2 nephrologists, 1 dietitian, and 10 primary nurses. Since the early 2000s, the prevalent continuous ambulatory PD patient load has increased by a factor of 10, from 40 to 400. The INPU was the first unit in China to develop a primary nursing model and an integrated care model in PD.

Correspondence to: M. Zhao, Renal Division, Peking University First Hospital, Institute of Nephrology, Peking University, Beijing 100034 PR China.

mhzhao@bjmu.edu.cn

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Strategies for information-based management and continuous quality improvement are applied in the routine work of the PD center. New nursing initiatives such as patient empowerment and self-care have also been successfully implemented in clinical practice. Our 5-year patient survival rate of 51% (8) is comparable, or even superior, to those of developed countries (9,10). Despite our patients being relatively old (mean age: 60 years), and many (40%) being diabetic, the peritonitis incidence is approximately 1 episode in 60 patient-months (11). The PD program also contributes to one of the main goals of the INPU: retarding the progression of renal dysfunction in chronic kidney disease and preventing dialysis-associated complications. Application of translational research makes it possible to generate improvements in patient care.

HOW TO OPTIMIZE THE EFFICIENCY OF CLINICAL RESEARCH IN PD?

During the continuous expansion in the number of PD patients for whom our center cares, the number of nephrologists and nurses did not increase. Consequently, one of the main challenges was to maintain excellent outcomes while simultaneously conducting high-quality research work with limited staff. We have been able to address this issue by adhering to these principles:

- Training the nephrologists, especially the leader of the PD center (who must be already adequately trained), to be able to act as physician–scientists who can raise scientific hypotheses based on routine clinical work
- Creating and maintaining a team of nurses characterized by enthusiasm and motivation for research
- Constructing and maintaining a clinical research platform, including the clinical database and bio-banks

necessary to facilitate both translational research and research funding

- Identifying research directions relevant for Chinese patients
- Implementing clinical research in a cost-efficient way

Although these strategies are organically combined, each strategy is also implemented and monitored within a continuous quality improvement program, which is therefore also a mandatory prerequisite for our clinical research.

The present review focuses on the foregoing strategies in explaining and describing the association between good clinical practice and efficient clinical research in the Chinese setting.

Strategy 1 — Training Physician-Scientists to Raise Scientific Hypotheses Based on Clinical Work:

Isolated from clinical practice, clinical research has no vitality and is neither long-standing nor applicable. A good clinical researcher must therefore be equipped with good research skills. Accordingly, INPU implemented an ambitious systematic training program for all clinicians engaged in advanced nephrology or in laboratory work. In general, during fellowship training, all young nephrologists identify their own specialty, which depends both on the demands of the academic direction of INPU and the individual's interests. With the guidance of a tutor, a series of specialized courses are then chosen. Young nephrologists are also encouraged to continuously follow the international literature of their specific chosen field. Clinical or basic research is initiated and performed in parallel with implementation of the clinical training program. After completion of fellowship training, some nephrologists are assigned to further academic training abroad. For example, one of our PD doctors was trained at the Karolinska Institute, Sweden, and another at the Hypertension and Nephrology Institute of Vanderbilt University, United States.

Early on, the current leader of our PD center, also a physician-scientist, raised a series of clinical issues in the PD field, one example being sodium restriction, widely recommended to the general population and patients with hypertension, cardiovascular disease, and chronic kidney disease. However, some of our PD patients complained of anorexia and spontaneously reduced their nutrient intake when prescribed a restricted sodium intake. We therefore hypothesized that a sodium intake that was too low might worsen nutrition status and increase the risk of death in PD patients. In a single-center cohort study, we confirmed that association and concluded that the benefit of sodium restriction is possibly outweighed by a decline in nutrient intake (6).

A second example concerns lean body mass (LBM), which is considered an index of muscle protein store and a biomarker for overall outcome in dialysis patients (12–14). The “gold standard” for LBM measurement is the tracer dilution method (15), which is laborious, invasive, and not suitable for routine patient care. Noninvasive and indirect methods such as creatinine kinetics, anthropometry, and bioelectrical impedance are therefore increasingly applied in PD. Based on the assumption that the prognostic value of a biomarker might be more important than its precision, we hypothesized that a method of LBM calculation that could independently predict mortality would therefore be more valuable for routine application. In a subsequent study, we were able to show that LBM deduced from creatinine kinetics, but not from anthropometry or bioelectrical impedance, was indeed an independent prognostic marker of mortality (7).

A third example is the early diagnosis of peritonitis. It has been demonstrated that the white blood cell (WBC) count in effluent on the 3rd day of treatment for peritonitis or a prolonged elevation in the WBC count during peritonitis constitutes a risk factor for an adverse outcome (16–18). Moreover, some causative organisms have also been found to correlate with failure of treatment for peritonitis (19). However, neither the effluent WBC count on day 3 nor the identification a specific causative organism is available at initiation of treatment for peritonitis. On the other hand, signs and symptoms of peritonitis—abdominal pain, fever, and cloudy fluid—are easily determined at onset. We therefore used a prospective cohort study to look for a possible association between disease severity score and peritonitis outcome. Our study revealed that the disease severity score was not linked to any of effluent WBC count, causative organism, or peritonitis outcomes in adult PD patients (11).

In summary, it is possible to raise scientific hypotheses based on clinical issues only if practitioners are diligent in their thinking and challenge the “routine” with an innovative spirit. Good research ideas often originate from routine clinical activities, such as during case discussions (when a specific case is analyzed historically in terms of diagnosis and treatment) or at quality management meetings (when center-based data are reviewed).

Strategy 2 — Building an Organized, Dedicated Team of Nurses with Research Enthusiasm and Motivation:

Under the influence of the traditional academic atmosphere within INPU, nephrologists at the PD center are not only motivated to initiate translational research, but also to organize a well-functioning team and to continuously motivate and, in various ways, support the team in conducting clinical research.

It is important to recognize the importance of all the PD nurses in the context of the clinical database. The major points of interest here are these:

- Assign a primary nurse to each new PD patient. The primary nurse constitutes the information center for the assigned patients, their family members, and clinicians. The primary nurse is responsible for promptly recording all patient-related data and for delivering relevant information to team members, including the physician, other nurses, the dietitian, and other team members such as the psychotherapist and physiotherapist. The nurse also provides suggestions to patients. This model ensures that many complications are prevented and treated in a timely manner.
- Delegate to the primary nurse responsibility for developing an individual chronic kidney disease management plan, including pre-dialysis education; pre-, peri-, and postoperative care; and follow-up at regular clinic visits. The nurse therefore functions as observer, recorder, and also coordinator of clinical research. Close contact with this nurse and mutual trust vis-à-vis patients and family members can also significantly improve the compliance of patients to prescriptions, advice, and if applicable, various study procedures.

In the early phase of our PD program, a few nurses engaged in clinical research subsequently recognized that the research was helpful for their medical career and for improving patient care. They started to share their experiences with other nurses, with the result that more nurses became involved in research. Currently, most primary nurses of our PD center are active researchers and do not simply play a support role in clinical research. For example, whether seasonal variation in blood pressure in dialysis patients (20) can be ameliorated using a given intervention is unknown. Our primary nurses observed that some patients did not display such variation if compliant to dietary fluid and sodium restriction and prescribed higher doses of antihypertensive medications during the cold season. In a self-controlled interventional study in 76 PD patients, we determined that intensive nursing care (including patient education on volume control), home blood pressure monitoring, and intensified antihypertensive treatment reduced the seasonal variation of blood pressure in PD patients (21). Those data provided evidence for the efficacy of implementing nurse-centered interventions, and in view of their great contributions to clinical research, our primary PD nurse team was awarded the highest level of the Science and Technology Award by the Chinese Nursing Association.

Strategy 3 — Constructing a Clinical Research Platform in Which Efficient Database and Bio-banks Facilitate Translational Research and Attract Research Funds:

In recent years, the INPU has developed a clinical research platform. It had become clear that, to conduct good clinical research, a clinical database and bio-banks are fundamental. Since the early 2000s, our PD center has enrolled more than 1000 incident PD patients as subjects in a prospective cohort study. We designed a series of forms for collecting the necessary data at baseline and at follow-up visits. In parallel, we collected, at regular intervals, bio-samples including serum, urine, and effluent within a digital computerized management system for further translational research. Based on this data-gathering, more than 20 peer-reviewed articles have been published in international journals including *Kidney International*, the *Clinical Journal of the American Society of Nephrology*, *Nephrology*, *Dialysis*, *Transplantation*, and *Peritoneal Dialysis International*. Those publications have, in turn, greatly facilitated the receipt of new research funds from the Beijing government, the Ministry of Education of China, the International Society of Nephrology, and international pharmaceutical companies such as Baxter and Fresenius Kabi.

Strategy 4 — Choosing Research Areas Appropriate for Chinese Patients and Implementing Clinical Research in a Cost-Efficient Way:

Although the dialysis population in China is large, most recommendations for the prevention and treatment of dialysis-associated complications are based on evidence deduced in studies of their Western counterparts. The result is that the guidelines do not take the specifics of PD in China into account and that Chinese PD experiences are not considered in the management of PD patients overseas. All the aspects of and understandings about complication management in China therefore need to be shared both domestically and internationally.

For example, PD-associated peritonitis contributes to technique failure and mortality. Although the International Society for Peritoneal Dialysis guidelines on the prevention of peritonitis have been broadly applied in most Western PD centers, there are doubts about the suitability of those recommendations for Chinese PD patients. The economic and hygiene status of PD patients vary broadly in the different regions of our country. Some patients with poor individual and environmental hygiene status might not follow the standard techniques during bag exchanges, resulting in the occurrence of peritonitis. It is therefore important to observe how bag exchanges are performed by PD patients and how training program procedures affect the peritonitis risk, individualizing

the training to appropriately fit the patient's ability and environment so as to minimize contamination during the exchanges.

In an observational cohort study, we found that, after 6 months of treatment, some PD patients no longer followed the exchange procedures taught at the initial training (22). We also found that the time to a first episode of peritonitis was significantly shorter in patients failing to wear a face mask or cap during exchanges (22). Those findings constitute one of the rationales for retraining as outlined in the International Society for Peritoneal Dialysis position statement on reducing the risk for peritonitis (23). Furthermore, we explored whether an alternative training method delivered by nurses affects the peritonitis risk. Based on an analysis from a cohort study, assisted patients did as well as autonomous patients in terms of peritonitis prevention if the patient and the family member were trained simultaneously at the start of PD (24). An important point was our observation that the peritonitis risk was lower in patients trained by PD nurses having advanced experience in general medicine than by nurses with less experience (25).

After the application of the above observations in our clinical practice, we continued to seek ways to further lower the peritonitis rate if possible. We therefore used a series of interventional studies to explore other potential methods for reducing the peritonitis or contamination risk. We designed a mini-PD house to prevent touch contamination during bag exchanges. That innovation was awarded a patent by the state intellectual property office of China. A 6-month prospective randomized controlled trial is currently underway to compare the peritonitis rate, quality of life, and physical activity of patients who do and do not use the mini-PD house. In addition, given that the optimal method and frequency for retraining PD patients is not yet determined, another randomized controlled study in three groups of patients ($N = 120$) is comparing retraining programs, with the peritonitis rate as the primary endpoint. The methods being compared are the current protocol (control), retraining using only verbal education methods, and retraining by performing bag exchanges in a physical one-to-one setting.

Another concern in clinical research is its financial aspects, from the perspectives of both the study and treatment costs. For example, the guideline recommendations for daily protein intake (DPI) in the nutrition management of PD patients is deduced from nitrogen balance studies, which were performed in small samples of Western subjects (26,27). However, the DPI actually reported in numerous observational studies around the world is lower than the recommendation (27–29), which makes nutrition management confusing. A new nitrogen

balance study with a larger sample size and a longer duration could potentially be performed to further explore the appropriate DPI, but we concluded that a large observational study would be more appropriate and cost-effective, and consequently, we conducted a 4-year study involving 305 patients. The DPI and daily energy intake were measured at baseline and repeatedly thereafter throughout the study period. During the study, we observed that a 24-hour DPI lower than 0.73 g/kg was associated with a higher risk of all-cause mortality, cardiovascular death, and time to a first peritonitis episode (30). Our current clinical practice has been changed accordingly.

FUTURE STRATEGIES

Although many of the findings emerging from our clinical research have generated multiple improvements in our clinical practice, we recognize the limitations of the research conducted so far. Most of the studies were single-center and observational in nature, including, for example, correlations of some routinely measured variables such as LBM, sodium intake and removal, DPI, peritoneal protein clearance, and outcome events, and did not provide novel hypotheses about the physiologic mechanisms of dialysis-related complications. Moreover, single-center observational studies normally do not provide evidence strong enough to affect international guidelines in PD. Our future directions therefore include

- collaboration with other physician-scientists—especially colleagues in clinical epidemiologic, immunologic, and genetic research groups within the INPU—to perform studies exploring potential mechanisms for dialysis-associated complications that will lead to enhancements in the treatment and prevention of such events.
- the performance of more multicenter, observational, and interventional studies, which will help to further adjust our preventive and therapeutic strategies for improving quality of life and survival in PD.

SUMMARY

We identified 4 aspects fundamental to good clinical research:

- Generation of scientific hypotheses related to optimization of patient care, raised by well-trained physician-scientists and originating from routine clinic work, must be the basis for all clinical research.
- The team of PD nurses must be adequately trained

and motivated to become an integral part of research activities.

- A platform, including a clinical database and biobanks based on the regular follow-up of all patients, is essential.
- Clinical research should be tailored to fit the country and center-specific environment and has to be conducted in a cost-effective manner.

It is our firm belief that, once these 4 pillars are present, they will allow for continuous expansion of data collection, which in turn will constitute a foundation for changes in PD practice, producing further improvements in outcomes.

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DISCLOSURES

The authors declare no financial conflicts of interest.

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