CardioRenal Medicine

Cardiorenal Med 2015;5:145–156
DOI: 10.1159/000380915
Published online: March 26, 2015

1664–3828/15/0052–0145$39.50/0
www.karger.com/crm

Review

Peritoneal Dialysis in Patients with Refractory Congestive Heart Failure: A Systematic Review

Renhua Lu[a, b] María-Jimena Muciño-Bermejo[b] Leonardo Claudino Ribeiro[b] Enrico Tonini[b] Carla Estremadoyro[b] Sara Samoni[b] Aashish Sharma[b] José de Jesús Zaragoza Galván[b] Carlo Crepaldi[b] Alessandra Brendolan[b] Zhaohui Ni[a] Mitchell H. Rosner[c] Claudio Ronco[b]

[a]Department of Nephrology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [b]Nephrology, Dialysis and Transplantation of the San Bortolo Hospital, International Renal Research Institute of Vicenza, Vicenza, Italy; [c]Division of Nephrology, University of Virginia Health System, Charlottesville, Va., USA

Key Words
Extracorporeal ultrafiltration · Heart function · Glomerular filtration rate · Hospitalization days

Abstract
Background: Refractory congestive heart failure (RCHF) is associated with a high mortality rate and is a major contributor to hospital admissions. Peritoneal dialysis (PD) is an option to control volume overload and perhaps improve outcomes in this challenging patient population. The aim of this systematic review is to describe the relative risk-benefit ratio based on data reported regarding the use of PD in RCHF. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. An electronic search of PubMed, Embase, and the Cochrane Library was performed to identify relevant studies published from January 1951 to February 2014. Eligible studies selected were prospective or retrospective adult population studies on PD in the setting of RCHF. The following clinical outcomes were used to assess PD therapy: (1) hospitalization rates; (2) heart function; (3) renal function; (4) fluid overload, and (5) adverse clinical outcomes. ***Summary:*** Of 864 citations, we excluded 843 citations and included 21 studies (n = 673 patients). After PD, hospitalization days declined significantly (p = 0.0001), and heart function improved significantly (left ventricular ejection fraction: p = 0.0013; New York Heart Association classification: p = 0.0000). There were no statistically significant differences in glomerular filtration rate after PD treatment in non-chronic kidney disease stage 5D patients (p = 0.1065). Among pa-

Claudio Ronco
Nephrology, Dialysis and Transplantation of the San Bortolo Hospital
International Renal Research Institute of Vicenza, Viale Rodolfi, 37
IT–36100 Vicenza (Italy)
E-Mail cronco@goldnet.it

tients treated with PD, body weight decreased significantly (p = 0.0006). The yearly average peritonitis rate was 14.5%, and the average yearly mortality was 20.3%. ***Key Messages:*** This systematic review suggests that PD may be an effective and safe therapeutic tool for patients with RCHF.

Introduction

Refractory congestive heart failure (RCHF) is a growing health problem and a major cause of mortality and morbidity in the world. It is also a leading cause of hospitalizations, rehospitalizations, and is associated with high costs.

Current guidelines [1] recommend diuretics as a first-line therapy for the treatment of RCHF. However, Fonarow et al. [2] reported that >20% of patients with RCHF did not have symptomatic improvement with this therapy. Moreover, diuretics use has been linked to worsening of kidney function and progression of RCHF [3]. Patients may also become resistant to diuretics or develop worsening renal function and electrolyte abnormalities that limit their use [4]. An alternative strategy in these challenging patients is ultrafiltration such as hemodialysis (HD) and peritoneal dialysis (PD). HD-derived modalities, such as aquapheresis, involve the placement of a catheter in the bloodstream that continuously runs the patient's blood through a filter (such as Aquadex System 100) to remove excess fluid. However, recent studies showed that there are several issues in the long-term use of aquapheresis in RCHF patients such as its being costly, inducing poor recovery of renal function [5], worsening anemia due to continuous blood loss and hemorrhage, and also being limited by patient transport difficulties to the dialysis centers [6].

Most recently, PD has been supported by several publications as another therapy for ultrafiltration in RCHF patients [7–10]. In 1951, the use of PD for RCHF was reported by Benhamou et al. [11]. The principal advantage of peritoneal ultrafiltration is the continuous, slow, and more physiologic removal of extracellular fluid with stable hemodynamics. This is also an attractive method due to its reasonable costs. PD is technically simple with fewer facility requirements, such as electricity or water treatment equipment. In the last 6 decades, several studies indicated that PD therapy in RCHF patients reduces hospitalization rates and mortality, improves quality of life, and has reasonable costs [12]. However, other studies demonstrated that application of PD in RCHF patients did not have a positive risk-benefit ratio due to complications like peritonitis [13]. With the recent publication of several studies as well as improvements in PD techniques, it seems reasonable to reassess the use of PD in patients with RCHF.

The main aim of this systematic review is to describe the relative risk-benefit ratio regarding the use of PD in RCHF.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org) [14]. All stages of study selection, data extraction, and quality assessment were performed independently by two reviewers (R.L. and M.-J.M.-B.). Any disagreement was resolved via discussion and consensus.

Literature Search

A systematic search of PubMed, Embase, and the Cochrane Library was performed to identify relevant studies published from January 1951 to February 2014. No language restrictions or geographical restrictions were applied.

The following terms, adapted for each database, were used for the searches: ('heart failure' OR 'HF') and ('peritoneal dialysis' OR 'PD' OR 'hemodialysis' OR 'HD' OR 'extracorporeal blood purification' OR 'EBP'). The related-articles function was also used to broaden the search, and the computer search was supplemented with manual searches of the reference lists of all retrieved studies, review articles, and conference abstracts.

Inclusion and Exclusion Criteria

All available full-text reviews were independently performed by two reviewers (R.L. and M.-J.M.-B.) and the following specific inclusion criteria were set before selecting articles: (1) prospective or retrospective design; (2) adult population (age ≥18 years); (3) diagnosis of RCHF, as defined by the 2013 ACCF/AHA Guideline for the management of heart failure [15]; (4) at least 10 patients treated with PD; (5) patients treated with PD, and (6) description of hospitalization, heart function, renal function, PD complications, or mortality.

Editorials, letters to the editor, case reports, meeting abstracts, and animal experimental studies were excluded.

Data Extraction

The data were extracted independently by two reviewers (R.L. and M.-J.M.-B.). Disagreements were resolved through discussion. The following information was extracted from each study: first author; year of publication; study design; country; follow-up period; number of patients in each study; characteristics and demographic features of the study population, and outcomes of interest (hospitalization, heart function, renal function, PD complications, and mortality). The number of withdrawals was also recorded.

Outcome Measures

The following clinical outcomes were used to assess PD therapy, either PD alone or combined PD and HD, in patients with refractory heart failure: (1) hospitalization rates: change in hospitalization days before and after PD; (2) heart function: left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) classification; (3) renal function: estimated glomerular filtration rate [eGFR; for this variable, patients were categorized into two groups: chronic kidney disease 5 dialysis (CKD5D) and non-CKD5D]; (4) fluid overload: weight and diuretics, and (5) adverse clinical outcomes: peritonitis rate and mortality.

Hospitalization rates were estimated as the difference in hospitalization days per year in the same group, before and after PD treatment. As not all of the articles reported peritonitis rates as episodes per year, we measured peritonitis frequency in terms of percentage of patients in the studied population that presented peritonitis per year.

Quality Assessment

The quality of each study was assessed using the scoring system of the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group ranging from zero (lowest quality) to twelve (highest quality; table 1; https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after.htm). The primary outcome of interest was the relative risk-benefit ratio based on reduction of hospitalization days associated with PD. Secondary outcomes included mortality, cardiac function, renal function, and complications related to PD (e.g. peritonitis).

Statistical Analysis

The main 'pre-post' variables of interest on which statistical analyses were based are:

- Hospitalization days
- Cardiac function: LVEF, NYHA classification
- Kidney function: eGFR
- Body weight
- Diuretic use

Some of these variables of interest, such as eGFR, were also compared in a subset of non-CKD5D stage patients.

The other variables of interest are:

- Mortality
- Complications related to PD (peritonitis)

The main aim of this analysis was to establish which of the 'pre-post' variables changed after dialysis. This was assessed by a meta-analysis in order to obtain a global p value for each of the variables using the

Table 1. Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group

First author, year [ref.]	Scale	Interpretation
Núñez, 2012 [44]	10	good
Hébert, 1995 [23]	9	good
Cnossen, 2012 [27]	8	fair
Núñez, 2012 [20]	9	good
Koch, 2012 [46]	9	good
Sánchez, 2010 [16]	9	good
Kunin, 2013 [8]	10	good
Gotloib, 2005 [17]	8	fair
Sheppard, 2004 [30]	7	fair
Courivaud, 2014 [45]	10	good
Ryckelynck, 1998 [22]	8	fair
Nakayama, 2010 [25]	8	fair
Sotirakopoulos, 2011 [24]	9	good
Stegmayr, 1996 [18]	8	fair
Bilora, 2002 [29]	8	fair
König, 1991 [19]	8	fair
Cnossen, 2010 [26]	8	fair
Bertoli, 2014 [10]	10	good
Rizkallah, 2013 [9]	8	fair
Takane, 2006 [21]	8	fair
Aggarwal, 2002 [28]	8	fair

0–4 = Bad; 5–8 = fair; 9–12 = good.

means and standard deviations estimated in each article; the articles were weighted using the scoring system of the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group.

The mean of each numerical variable *X*, μ_x, of the study is estimated by the weighted mean of means

$$\widehat{\mu_x} = \frac{\sum_{i=1}^{n_{\mu_x}} I_i \overline{X}_i}{\sum_{i=1}^{n_{\mu_x}} I_i},$$

where $\overline{x}_i$ is the mean of *X* estimated in the i-th article. Obviously, only articles where $\overline{x}_i$ is present can be considered for estimating μ_x: the number of the abstracted articles is n_{μ_x}. Analogously, the standard deviation σ_x of the variable *X* is estimated by the weighted mean of standard deviations

$$\widehat{\sigma_x} = \frac{\sum_{i=1}^{n_{\sigma_x}} I_i s_i}{\sum_{i=1}^{n_{\sigma_x}} I_i},$$

where s_i is the standard deviation of *X* estimated in the i-th article. Obviously, only articles where s_i is present can be considered for estimating σ: the number of these articles is n_{σ_x}.

The level of statistical significance in every analysis was set at $p < 0.05$. Analyses were performed with R, version 3.1.2 (October 2014).

Results

Characteristics of Eligible Studies

We used the PRISMA 2009 Flow Diagram to select articles (www.prisma-statement.org). The initial search yielded 863 potentially relevant articles after 1 duplicate had been removed, and a total of 829 studies were excluded after abstract review. On full-text review of 34 articles, 13 of them did not meet the eligibility criteria: 8 were case reports, 3 studies included less than 10 patients, and 2 studies with PD and HD were not focused on RCHF (fig. 1).

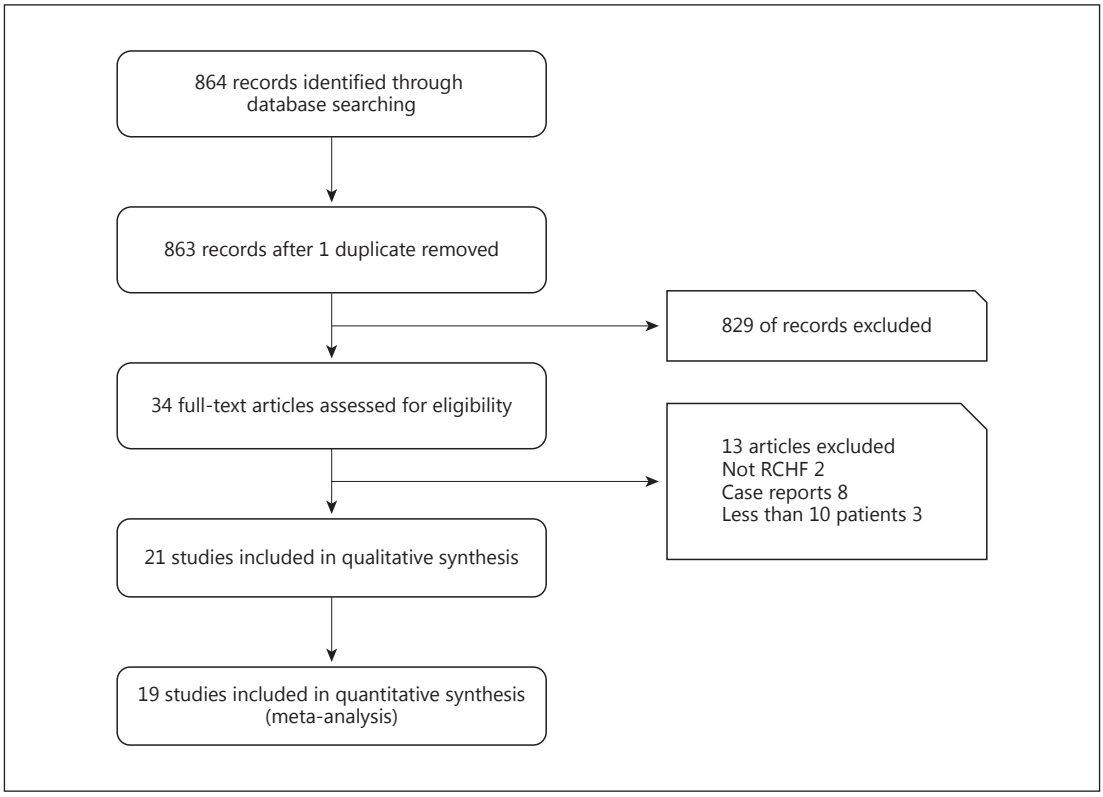

Fig. 1. Flow chart of article selection (PRISMA 2009 Flow Diagram).

Twenty-one of 864 articles were selected, including 14 prospective studies and 7 retrospective studies. Among these articles, 13 were from Europe, 5 from Asia, and 3 from North America. The total number of patients was 673, the mean age was 67.4 ± 10.1 years, and the mean percentage of males was 69.2%. The mean follow-up time was 33.2 months (table 2).

PD Techniques

Details of the PD technique were often not reported. Where data were available, 5 studies used Tenckhoff catheters [8, 16–19]. The dialysate utilized was dextrose (6 studies) [17, 19–23], icodextrin (2 studies) [9, 24], and dextrose or icodextrin (5 studies) [10, 16, 25–27]. The PD dose was not available for all studies.

Study Outcomes

Hospitalization Rates

Fourteen studies (66.67%; n = 416) were included in the meta-analysis examining the difference in hospitalization days between pre- and post-PD treatment. Hospitalization days significantly declined almost 5.08 days/year after PD treatment (6.30 vs. 1.22 days/year; p = 0.0001; fig. 2; table 3).

Heart Function

Almost all enrolled studies used LVEF and the NYHA classification to evaluate heart function between pre- and post-PD ultrafiltration. Thirteen studies (61.90% used LVEF and the NYHA classification; n = 537) were included in the meta-analysis examining the difference

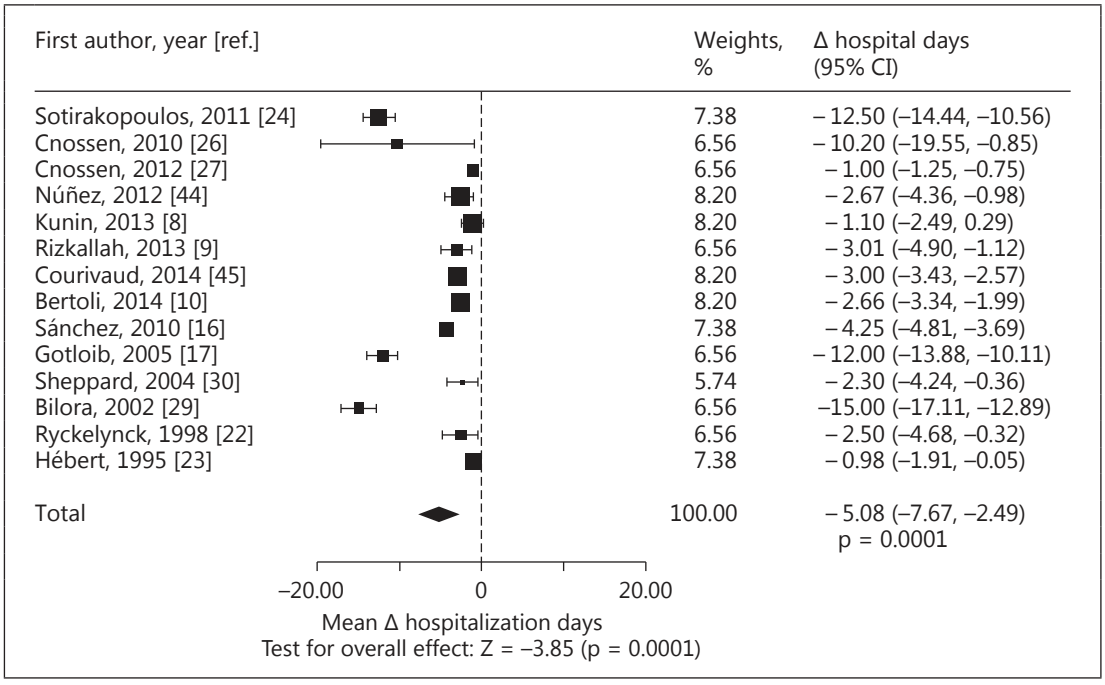

Fig. 2. The difference in hospitalization days between pre- and post-PD treatment.

Table 2. Characteristics of studies that included basic features, complications, and mortality

First author, year [ref.]	Follow-up, months	Patients, n	Males, %	Age, years	Peritonitis, year %	Mortality, year %
Nakayama, 2010 [25]	27.7	12.0	58.3	81±6	3.6	10.8
Sotirakopoulos, 2011 [24]	78.0	19.0	n.a.	71.3±8.1	1.6	28.3
Cnossen, 2010 [26]	120.0	24.0	75.0	67±10	1.7	8.3
Cnossen, 2012 [27]	40.0	23.0	73.9	66.1±21.9	7.5	9.0
Núñez, 2012 a [20]	16.0	62.0	33.9	77±n.a.	n.a.	21.1
Núñez, 2012 b [44]	14.0	25.0	72.0	75.1±n.a.	37.7	2.0
Kunin, 2013 [8]	42.0	37.0	73.0	66±n.a.	32.0	39.5
Rizkallah, 2013 [9]	48.0	10.0	70.0	58.3±12.7	7.5	15.0
Courivaud, 2014 [45]	50.7	126.0	69.0	72±11	6.2	18.7
Bertoli, 2014 [10]	24.0	48.0	81.3	74±9	26.7	22.0
Sánchez, 2010 [16]	24.0	17.0	64.7	64±9	2.0	22.0
Koch, 2012 [46]	13.3	118.0	60.2	73.2±11.4	4.8	45.0
Takane, 2006 [21]	12.0	16.0	81.3	66.3±2.8	n.a.	0.0
Gotloib, 2005 [17]	19.8	20.0	n.a.	65.7±7.7	27.0	18.2
Sheppard, 2004 [30]	12.0	19.0	63.2	63.2±n.a.	n.a.	36.8
Aggarwal, 2002 [28]	n.a.	20.0	n.a.	n.a.	n.a.	n.a.
Bilora, 2002 [29]	n.a.	16.0	87.5	56.7±3.2	n.a.	n.a.
Ryckelynck, 1998 [22]	12.7	15.0	73.3	66.7±n.a.	12.6	44.1
Stegmayr, 1996 [18]	18.5	16.0	n.a.	60±14	n.a.	24.3
Hébert, 1995 [23]	24.0	17.0	70.6	51.6±14.9	23.5	18.0
König, 1991 [19]	34.3	13.0	n.a.	n.a.	n.a.	0.0
Mean	33.2	33.7	69.2	67.4±10.1	14.5	20.3

n.a. = No data available.

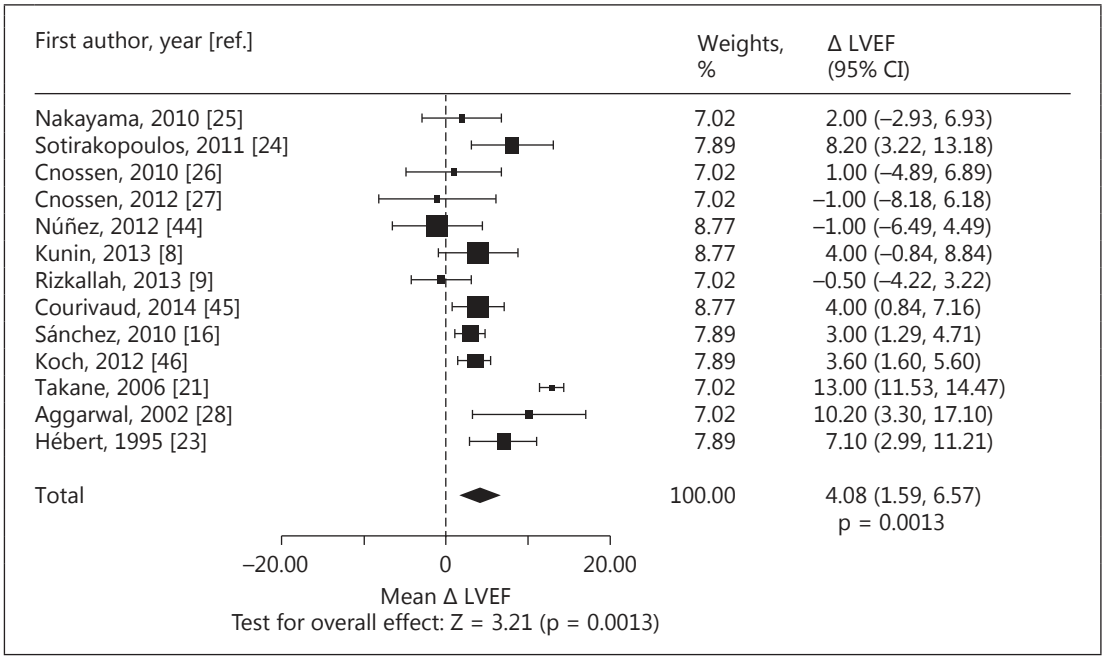

Fig. 3. The difference in LVEF between pre- and post-PD treatment.

Table 3. Comparison of pre- and post-PD treatment

Parameter	Studies, n	Studies used, %	Weights used, %	Pre-PD	Post-PD	Δ	p value
Weight (kg)	12	57.14	58.89	73.37	69.71	–3.66	0.0006
Diuretics (mg/day)	5	23.81	25.56	246.28	252.60	6.33	0.7387
GFR (ml/min)	8	38.10	40.56	29.93	24.90	–5.03	0.0118
GFR, only non-CKD5D (ml/min)	6	28.57	30.56	24.89	21.88	–3.01	0.1065
LVEF (%)	13	61.90	63.33	34.78	38.86	4.08	0.0013
NYHA	15	71.43	70.55	3.53	2.17	–1.37	0.0000
Hospital days/year	14	66.67	67.78	6.30	1.22	–5.08	0.0001

in LVEF between pre- and post-PD ultrafiltration. LVEF was significantly improved almost 4.08% after PD ultrafiltration (34.78 vs. 38.86%; p = 0.0013; fig. 3; table 3). We found that after PD ultrafiltration, the NYHA score was reduced significantly (3.53 vs. 2.17; p = 0.0000; table 3).

Renal Function

Eight studies (n = 335) included CKD1–5D patients; a meta-analysis was done on the eGFR difference between pre- and post-PD treatment. We found that GFR was significantly decreased (29.93 vs. 24.90 ml/min; p = 0.0118; table 3). However, in 6 studies (n = 282) which only included non-CKD5D patients with greater residual renal function, we found that eGFR was not statistically different after PD treatment (24.89 vs. 21.88 ml/min; p = 0.1065; fig. 4; table 3).

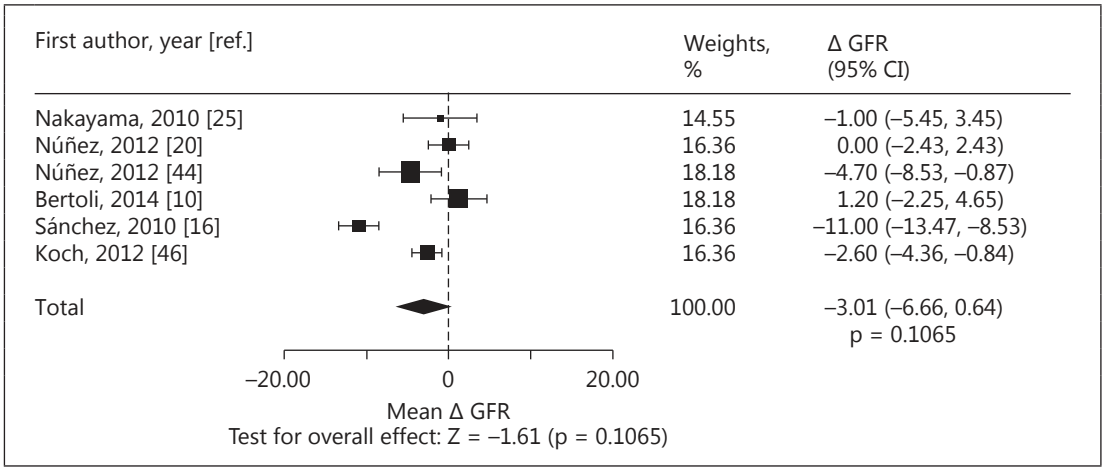

Fig. 4. The difference in GFR between pre- and post-PD treatment based on non-CKD5D patients.

Fluid Overload

Body weight also decreased significantly after PD ultrafiltration (73.37 vs. 69.71 kg; p = 0.0006; table 3). However, the diuretic dose was not statistically different after PD treatment (246.28 vs. 252.60 mg; p = 0.7387; table 3).

Adverse Clinical Outcomes

Two studies [28, 29] did not report mortality. The mean mortality rate of 19 studies was 20.3% per year. Seven studies did not report complications associated with PD [18–21, 28–30]. However, the mean incidence of peritonitis in 14 studies was 14.5% per year (table 2). Noninfectious complications of PD treatment such as procedure-related complications (i.e. bleeding) were seldom reported and, thus, we could not perform a specific analysis because of lack of standardized complication reports. From 21 studies, only 7 indicated the rate of noninfectious complications: 2 studies reported hypotension (with an incidence of 20 and 13.8%, respectively), 2 reported catheter dysfunction (with an incidence of 25 and 8.4%, respectively), 2 reported nonspecified noninfectious complications (with an incidence of 12 and 40%, respectively), and 1 reported an ultrafiltration failure incidence of 8.3%.

Discussion

We performed a systematic review of the efficacy of PD in adult patients with RCHF and identified 21 studies from 13 countries. This review represents a total of 673 patients. Moreover, in order to evaluate the quality of each study, we used the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (table 1).

This systematic review yielded three main findings. First, the fact that PD is associated with fewer hospital days indicated that PD can reduce health-care costs of RCHF patients (even accounting for the cost of the procedure). For many countries, heart failure is now the dominant cause of acute hospital admission [31]. In the USA, heart failure was responsible for 1 million hospital admissions per year between 2000 and 2010 [32, 33]. Furthermore, there is a rise in the prevalence of those patients suffering from symptomatic end-stage heart failure refractory to available therapies [34–36]. Survival of patients with RCHF is <50% at 6 months

[36]. Thus, RCHF is increasingly a major public health and financial problem. In this systematic review and meta-analysis, we found that after PD treatment, hospitalization days significantly declined by almost 5.08 days/year. In the study by Sánchez et al. [16], the sum of the costs borne by the patients in PD programs reached EUR 16,440, which is lower than the costs of continuing a conservative diuretic treatment plan (EUR 27,551; p = 0.095). Furthermore, in this study, PD was associated with a higher cost utility than conservative therapy. Coupled with the lower costs of PD, the cost utility for PD was EUR 23,305/quality-adjusted life year (QALY), while for conservative treatment it was EUR 81,053/QALY [16]. In the early 1980s and 1990s, some case reports (<10 patients) of PD in RCHF also suggested using intermittent PD such as 1 or 2 nightly exchanges to achieve the desired volume of ultrafiltration. Such curtailed PD therapy regimen could have a greater impact on quality of life and the cost of therapy for RCHF patients [37, 38]. Consequently, physicians should consider offering PD to appropriate patients in the hope of achieving a better quality of life due to fewer hospitalization days as well as reduced health-care costs.

Second, PD can improve heart function and can preserve residual renal function in non-CKD5D patients. Patients with rapidly worsening cardiac function can present with renal vasoconstriction and resistance to diuretics and concomitant refractory congestion. PD is highly effective in producing ultrafiltration [39]. This mechanism may improve cardiac output due to changes in the Frank-Starling curve, an increased left ventricular diastolic inflow, and an improvement in lung compliance after removal of the excess fluid [40]. This systematic review showed that after PD ultrafiltration, heart function significantly improved, as evaluated by LVEF and NYHA status. Patients' weight also decreased significantly with ultrafiltration.

It has been suggested that PD might also have other beneficial effects beyond volume removal. Indeed, one of the potential benefits of these therapies might be the avoidance of adverse renal effects of high-dose diuretics, namely, increased renin-angiotensin-aldosterone axis stimulation and activation of the sympathetic nervous system [41] which may lead to worsening kidney function. In this systematic review, we found that eGFR was stable after PD treatment in non-CKD5D patients, although the diuretic dose was not statistically significantly different after PD treatment. This systematic review verified whether PD can preserve residual renal function in non-CKD5D patients which may be the key in improving survival and cardiovascular outcomes in these patients [42]. Theoretically, PD ultrafiltration has been suggested to remove inflammatory cytokines as well as improving neurohormonal activation. This may lead to the restoration of responsiveness to diuretics [43]. However, we did not find any significant differences in diuretic dose before and after PD [9, 24, 44–46].

Third, the complication rate, such as peritonitis, was similar to that of patients who underwent standard chronic PD. As there are variable time units for measuring peritonitis rates among different studies, we standardized the incidence unit as the percentage of patients with peritonitis per year [47]. In this systematic review, we found that the yearly peritonitis incidence among patients undergoing PD for treatment of RCHF was not higher (14.5%) than the reported rate in ESRD patients, in whom peritonitis rates have been described to be as high as 51.1% in large series of patients [48].

Thus, our results suggest that PD, when used as a rescue therapy for RCHF, is as safe as it is when used as a standard treatment for ESRD [49, 50].

Limitations

Limitations of this study include the lack of prospective randomized controlled trials, comparative data among PD and HD as extracorporeal renal replacement therapy for RCHF, and the inclusion of 2 studies in which both HD and PD were used without comparing clinical outcome achieved with these two techniques.

Also, we included pre-post studies, in which it cannot be answered whether participants' improvement or deterioration would have occurred. Because there is no reference to a comparison group, we cannot absolutely affirm the effectiveness of the intervention. However, clinical data show that PD has been used in RCHF patients with subsequent improvement in the reports of clinical outcomes.

Moreover, as data on the pharmacological treatment were not mentioned in the included studies, we cannot confirm that every observed change in the clinical outcomes is fully attributable to PD treatment. Furthermore, as weight itself is not a perfect biomarker of volume status, we cannot affirm that body weight decline is absolutely not related to loss of muscle mass or malnutrition, since we do not have more objective markers of fluid balance, such as bioimpedance.

Finally, although it is conceivable that overall health-related costs are reduced as hospitalization days decrease, this systematic review is not designed to be a cost-benefit or cost-efficacy analysis; we cannot make any affirmation on the economic impact of PD on RCHF treatment.

Conclusions

In conclusion, this systematic review suggests that PD may be an effective and safe therapeutic option for improving heart function and weight control in patients with RCHF. PD has been reported to reduce hospitalization days and improve heart function, without worsening renal function, and to have acceptable rates of complications such as peritonitis. Physicians who treat patients with RCHF could consider offering this treatment.

Nevertheless, the statistical limitations of this review and the inherent limitations of the included studies should be considered, and conclusions drawn from our pooled results should be interpreted with caution. Future large-volume, well-designed randomized controlled trials with extensive follow-up are awaited to confirm and update the findings of this analysis.

Acknowledgements

The authors would like to thank the investigators of the included studies who provided copies of their papers and additional information on their studies. The authors wish to acknowledge that this systematic review was initiated during the international fellowship of R.L. at the Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy, and C.R. is the department director.

Disclosure Statement

None of the authors have any conflicts of interest to declare.

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