ORIGINAL ARTICLES

PERITONEAL RESTING WITH HEPARINIZED LAVAGE REVERSES PERITONEAL TYPE I MEMBRANE FAILURE. A COMPARATIVE STUDY OF THE RESTING EFFECTS ON NORMAL MEMBRANES

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◆ **Background:** Ultrafiltration failure (UFF) is a serious complication of long-term peritoneal dialysis (PD). Peritoneal rest (PR) has been demonstrated as a valid treatment to reverse the functional changes that occur in UFF. The effects of PR on a normally functioning human peritoneum are unknown but are expected to be neutral. Our hypothesis was that PR positively modifies peritoneal function in patients with UFF, in contrast to the absence of effects when PR is applied under normal conditions.

◆ **Patients and Methods:** We studied 84 PR periods, comparing 35 patients with UFF and 49 controls (resting for abdominal surgery with temporary discontinuation of PD). We analyzed peritoneal transport pre-PR and post-PR by calculating the mass transfer coefficients of creatinine (Cr-MTAC), the dialysate/plasma creatinine ratio (D/P Cr) and the ultrafiltration (UF).

◆ **Results:** Baseline data was similar for the 2 groups, although the UFF group had a longer median time in PD (39 [18 – 60] vs 10 [5 – 23] months; $p = 0.00001$). Peritoneal rest induced a decrease in D/P Cr, Cr-MTAC and an increase in UF capacity in the UFF group ($p = 0.0001$, $p = 0.004$ and $p = 0.001$, respectively), without causing changes in the control group. Peritoneal rest in patients with more than 6 months of UFF was not able to reduce peritoneal solute transport or improve UF capacity. Response to PR did not differ among UFF patients with or without a previous history of peritonitis. Peritoneal rest enabled patients with UFF to continue on PD for a median time of 23 months (range, 13 – 46 months).

◆ **Conclusions:** Peritoneal rest induces functional changes in patients with UFF but not in those with no functional abnormalities. This demonstrates that PR works only when abnormal but reversible functional conditions are present. However, the effect is highly dependent on how early PR is applied.

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Long-term exposure to peritoneal dialysis (PD) can lead to morphological and functional abnormalities in the human peritoneum, which occur in approximately one-third of patients treated with PD for more than 4 years (1,2). The most common functional change is type I ultrafiltration failure (UFF), which limits PD performance (1,2) and can lead to peritoneal sclerosis (3,4). Ultrafiltration failure is a serious problem that can cause overhydration, thereby increasing the risk for cardiovascular death (5,6).

The anatomical substrate of UFF is characterized by angiogenesis and epithelial-mesenchymal transition of the mesothelial cell, accompanied by loss of surface mesothelium and interstitial fibrosis in omental tissue (7–9). The contribution and potential reversibility of each of these processes remain to be determined, but once UFF is established, the therapeutic options are limited. These options include the use of nonglucose-based PD fluids such as icodextrin, transitioning to automated

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PD (APD) and electively switching to hemodialysis (HD) (1,2,10).

Our group has proposed peritoneal rest (PR) for UFF treatment as an approach to partially reverse transport changes (11–13). Rodriguez *et al.* have also confirmed this finding, specifying that PR should be performed as soon as the changes in permeability are documented, in order to improve the results (14). Animal models have also confirmed that PR in rats helps recover ultrafiltration (UF) capacity, reduces permeability and reverses some of the structural changes such as parietal peritoneal thickening and mesenteric fibrosis and angiogenesis (15,16).

Our hypothesis was that PR with intermittent heparinized lavages should reverse the functional alterations in patients with UFF, whereas it should have no effect on normally functioning peritonea. The aim of our study was to determine the effects of PR on patients with acquired UFF and to compare them with patients who had undergone resting under different clinical situations with no peritoneal transport abnormalities. We also analyzed the exposure to glucose-based PD fluids, its changes after PR and the factors that can influence the efficacy of PR among UFF patients.

PATIENTS AND METHODS

We studied all PR episodes performed in our PD unit between January 1988 and May 2013. These episodes were divided into 2 groups, those clinically indicated due to UFF and those performed for other reasons (these cases were named “controls”). Data were retrospectively collected but the study was designed prospectively. After performing several therapeutic PRs, we decided to study the effects of mandatory PR in patients without peritoneal transport abnormalities. Demographic data were collected from medical charts.

Between 1988 and 1998, patients were assigned to PR if they presented clinical evidence of a significant decrease in UF over time or insufficient UF to achieve volume control, coupled with the presence of fast low molecular weight (LMW) solute transport (defined as an elevated peritoneal mass transfer area coefficient of creatinine [Cr-MTAC] greater than 14 mL/min [17]). After 1998, the criteria for UFF were clearly established by the International Society for Peritoneal Dialysis (ISPD); patients were diagnosed with UFF if they presented a negative balance < 400 mL after a 2-L 3.86/4.25% glucose exchange with 4 h of dwell time, associated or not with high transport status.

Patients with a recent history (in the last 4 weeks) of peritonitis were excluded. The control group included

those patients with a PR performed due to intra-abdominal surgery requiring a temporary discontinuation of PD. These patients had normal LMW solute peritoneal transport without UFF prior to PR.

EVALUATION OF MEMBRANE TRANSPORT STATUS

Low molecular weight solute transport was determined by a peritoneal equilibrium test (PET), which has been performed regularly in our unit since 1981. The PET consists of a 4-h dwell time glucose exchange, taking peritoneal effluent and blood samples to calculate the peritoneal mass transfer area coefficient of urea (U-MTAC, mL/min) and creatinine (Cr-MTAC, mL/min) using a previously described mathematical model (18). Initially, PET was performed using a 1.36% glucose exchange with 3 blood and 10 effluent samples; this methodology changed over time, switching to a 2.27% glucose exchange in the 1990s and finally to 3.86/4.25% in 2000, taking 6 effluent samples and 1 blood sample.

Initially, patients were asked to record daily UF, thereby enabling the calculation of a median daily UF. Patients used a 2-L 3.86/4.25% glucose exchange for 4–5 hours daily, which provided a measurement of UF and enabled us to follow changes over time. After 2000 and due to the changes in PET, UF was calculated on the basis of net balance (weighing the bag after drainage) after a 2-L 3.86/4.25% glucose exchange with 4-h dwell time during PET (19). Each patient served as their own control to evaluate the effects of PR on UF capacity. The methodology was simple, and UF was equally measured in each case.

PERITONEAL RESTING PROTOCOL

Peritoneal resting consisted of the discontinuation of PD for at least 1 month and the temporary transfer to HD performed through a permanent central venous catheter. During this month, peritoneal lavages were performed weekly or biweekly with the infusion of 100–200 mL of 1.36% glucose exchange with 3,500 to 5,000 UI of sodium heparin.

Peritoneal functional data (U-MTAC, Cr-MTAC, creatinine dialysate/plasma ratio [Cr-D/P] and UF capacity) were collected from PETs performed immediately before and after PR. Changes in peritoneal functional data pre-PR and post-PR were compared in the 2 groups; glucose overexposure was also evaluated. To quantify the exposure to glucose, we calculated the percentage of exchanges performed using 2.27% and 3.86% glucose PD fluids, using the same methodology for continuous ambulatory PD (CAPD) and APD patients.

We defined overexposure to glucose-based PD solutions when patients used more than 75% of 2.27% glucose exchanges or more than 25% of 3.86% glucose out of the total number of exchanges, both for CAPD and APD. The global number of exchanges under APD was superior to that on CAPD, by definition. Changes in glucose exposure after PR were evaluated; a 25% or greater decrease in the use of 3.86% glucose PD fluids or a 50% or greater decrease in the use of 2.27% glucose PD fluids was considered a significant reduction in glucose exposure after PR.

All patients' previous history of peritonitis was recorded, which was defined as the number of episodes and accumulated peritoneal inflammatory days (defined as the number of days with active peritoneal effluent inflammation [white blood cell count >100/ μ L] measured every other day until peritonitis resolution or catheter removal) (18). For the UFF group, the time from the last peritonitis episode to PR, the number of peritoneal inflammatory days, the causal germ, the severity of the last peritonitis episode (defined as the need for catheter removal) and the time intervals from PET (pre- and post-) to PR were also recorded.

The time from the diagnosis of UFF (documented by PET) to PR was also evaluated. Patients in the UFF group were divided into 2 subgroups; those cases with a diagnosis of UFF more than 6 months prior to PR (documented in 2 consecutive PETs) were classified as prior-UFF cases and those diagnosed less than 6 months prior to PR were classified as recent-UFF cases. The outcomes of these subgroups were also compared.

STATISTICAL ANALYSIS

All data were processed using the software program SPSS (Version 15.0.1, Chicago, IL, USA). Values are expressed as percentages and means ($\pm$ SD) or medians (range) when the distribution was not normal. Percentages were compared using the chi-square test, and the means and medians were compared using the Student *t*-test for nonpaired data or the Mann Whitney test, respectively. A value of $p < 0.05$ was considered statistically significant. Comparisons between groups were conducted by fitting a linear regression to the repeated measures in each group and by comparing the slopes of the corresponding regression lines.

RESULTS

BASELINE CHARACTERISTICS

Eighty-four PR episodes were identified, 35 in the UFF group and 49 in the control group. In the UFF group, 22 (62.85%) patients were diagnosed using clinical and functional criteria before 1998, and 13 (37.14%) were diagnosed after this date using the ISPD criteria for UFF. Baseline demographic characteristics were similar in the 2 groups (Table 1), although the UFF group showed a longer median time in PD before PR (39 [18 – 60] vs 10 [5 – 23] months; $p = 0.00001$) and a higher exposure to glucose prior to PR (35 [100%] vs 18 [36.73%]; $p = 0.00001$). No differences in exposure to low-glucose degradation product PD fluids, icodextrin or peritonitis

TABLE 1
Demographic Characteristics and Data on Peritoneal Rest

	UFF Group (<i>n</i> =35)	Controls (<i>n</i> =49)	<i>p</i>
Age, Median (IQ range) (years)	49 (34–62)	59 (42–68)	NS
Gender, Females, <i>n</i> (%)	14 (40)	14 (28.57)	NS
Diabetes, <i>n</i> (%)	9 (25.71)	8 (16.32)	NS
Time on PD, Median (IQ range) (months)	39 (18–60)	10 (5–23)	0.00001
Exposure to low GDP PD fluids, <i>n</i> (%)	4 (12.9)	11 (28.94)	NS
Icodextrin, <i>n</i> (%)	8 (22.85)	22 (44.89)	NS
Peritonitis, <i>n</i> (%)	20 (57.14)	22 (44.89)	NS
Cumulative days of peritonitis, Median (IQ range) (days)	6 (3–12)	2 (3–7)	NS
Duration of PR, Median (IQ range) (days)	30 (30–33)	30 (30–30)	NS
Overexposure to glucose, <i>n</i> (%)	35 (100)	18 (36.73)	0.00001
Overexposure to glucose after PR, <i>n</i> (%)	35 (100)	17 (34.69)	0.00001
Reduction in glucose exposure after PR, <i>n</i> (%)	19 (55.88)	7 (14.28)	0.00001
Time on PD after PR, Median (IQ range) (months)	23 (13–46)	18 (11–41)	NS

UFF = ultrafiltration failure; IQ = interquartile range; PD = peritoneal dialysis; GDP = glucose degradation products; PR = peritoneal rest; NS = not significant.

were found. Functional peritoneal data collected before PR showed significantly higher U-MTAC, Cr-MTAC and Cr-D/P and lower UF capacity in the UFF group when compared with the controls (Table 2).

In the UFF group, the median time from PET to PR initiation was 55 days (range, 15 – 73 days), and post-PR PET was performed after a median time of 16 days (range, 13 – 31 days).

EVOLUTION OF PERITONEAL TRANSPORT PARAMETERS PRE-PR AND POST-PR IN PATIENTS WITH UFF AND CONTROL PATIENTS

After PR, patients in the control group showed no differences in peritoneal functional parameters (Table 2). However, patients in the UFF group showed a significant decrease in solute transport (U-MTAC, Cr-MTAC, and Cr-D/P) and an increase in UF (Table 2). This behavior was significantly different from the control group (Figure 1). After PR, 11 patients (31.42%) in the UFF group completely normalized LMW solute transport (with a Cr-MTAC below 12 mL/min considered normal), and 24 patients (68.57%) showed partial recovery of LMW solute transport. The control group continued to show a significant lower solute and greater water peritoneal transport than the patients with UFF.

GLUCOSE EXPOSURE AFTER PR

An overexposure to glucose-based PD fluids was present in 100% of patients with UFF and 36.73% of controls prior to resting ($p = 0.00001$). There was a decrease in the use of glucose-based PD fluids in 55.88% of patients with UFF and 14.28% of controls after the procedure ($p = 0.00001$), although 100% of the patients with UFF and

34.69% of the controls were still overexposed to glucose after PR.

FACTORS INFLUENCING THE RESPONSE TO PERITONEAL RESTING IN PATIENTS WITH UFF

UFF longevity: The time from clinical diagnosis of UFF to PR was measured for all patients; 20 patients (57.14%) were classified as recent UFF (less than 6 months from diagnosis to PR) and 15 (42.85%) as prior UFF. The response was more favorable in this first group. In the recent UFF group, there was a significant decrease in Cr-MTAC and D/P Cr and an increase in UF, while in the prior UFF subgroup there was a trend towards increasing UF and decreasing hyperpermeability, but this was not statistically significant (Table 3).

Previous peritonitis: In the UFF group, 20 patients had a previous history of peritonitis, with a median number of 1 episode (range, 1 – 2). The median time from the last peritonitis to PR was 338 days (range, 126 – 567 days). When analyzing the last episode of peritonitis, the median number of peritoneal inflammatory days was 3 (3 – 5 days), with 20% of patients requiring catheter removal due to severe peritonitis. The reported causes of peritonitis were *S. aureus* in 20%, sterile in 25%, other gram-positive bacteria in 40%, polymicrobial in 10% and *P. aeruginosa* in 5%.

When comparing the evolution of peritoneal functional parameters pre-PR and post-PR in UFF patients with ($n, 20$) and without previous peritonitis ($n, 15$) and according to the repeated measures analysis, we found no differences in the evolution of peritoneal functional parameters. Both groups had a statistically significant

TABLE 2
Peritoneal Transport Data Before and After Peritoneal Rest in Patients with Ultrafiltration Failure and in Control Patients

		UFF Group ($n=35$)		Controls ($n=49$)		
			p		p	p
Cr-MTAC (mL/min)	Pre-PR	17.7±3.4	0.004	8.9±3.8	NS	0.0001
	Post-PR	15.4±4.7		9.4±2.8		0.0001
U-MTAC (mL/min)	Pre-PR	26.9±4.4	0.002	21.4±7.1	NS	0.0001
	Post-PR	23.7±6.1		21.8±4.8		NS
UF (mL)	Pre-PR	364.7±150.0	0.0001	765.0±269.6	NS	0.0001
	Post-PR	591.2±263.2		728.2±241.4		0.019
D/P Cr	Pre-PR	0.86±0.06	0.003	0.70±0.08	NS	0.0001
	Post-PR	0.82±0.08		0.71±0.08		0.0001

UFF = ultrafiltration failure; Cr-MTAC = mass transfer area coefficient creatinine; U-MTAC = mass transfer area coefficient urea; UF = ultrafiltration; D/P Cr = dialysate/plasma creatinine ratio; PR = peritoneal rest; NS = not significant.

Figure 1 — Evolution of peritoneal functional data before and after peritoneal rest in the control and ultrafiltration failure groups. (A) Creatinine MTAC (mL/min), (B) Urea MTAC (mL/min), (C) D/P-Cr and (D) UF/4 h (mL). The *p* value in bold expresses the differences between groups in the comparison of the gradients. Posthoc analysis showed statistically significant ($p < 0.05$) differences in all parameters evaluated when the 2 groups were compared. Cr-MTAC = mass transfer area coefficient creatinine; U-MTAC = mass transfer area coefficient urea; D/P Cr = dialysate/plasma creatinine ratio; UF/4h = ultrafiltration capacity; PR = peritoneal rest; UFF = ultrafiltration failure; NS = not significant.

increase in UF and a decrease in small solute transport; the decrease did not reach statistical significance in the peritonitis group (Figure 2).

MEDIUM-TERM OUTCOMES

In the UFF group, 3 patients were immediately transferred to HD after PR due to persistent UFF, and 2 patients underwent kidney transplantation. The remaining 30 patients continued on PD for a median time of 23 months (range, 13 – 46 months), which was similar to the patients in the control group who remained in PD for 18 months (range, 11 – 41 months) ($p = 0.33$).

DISCUSSION

According to our results, PR is an effective approach for completely or partially reversing the process known as UFF type I. The specific effects of PR in this situation are demonstrated by the lack of response when performed in patients with no peritoneal transport disorders.

This procedure enables the recovery of the peritoneal membrane, increasing water and decreasing LMW solute transport. Exposure to glucose-based PD fluids shows a reduction after PR, which is an indirect sign of the benefit of PR for UFF patients. The lack of changes in patients with normal LMW solute peritoneal transport without UFF reinforces the idea that PR exerts determinant effects on the morphological changes that take place in UFF. Similar findings have been reported in animal models. Kim *et al.* found that PR recovered UF and reduced permeability and parietal peritoneal thickening in rats (16). In 2005, Zareie *et al.* found that PR reduced angiogenesis in the mesentery and fibrosis in the parietal peritoneum, with a complete recovery of the mesothelial layer (15). In humans, PR for the treatment of UFF was first reported by our group in 1993, showing partial recovery of UF and decreased Cr-MTAC and U-MATC in 25 PRs performed in 16 patients (11). These findings were confirmed by Rodrigues *et al.*, who also suggested that the early application of PR after the diagnosis of UFF could further improve results (14). In agreement with this suggestion,

TABLE 3
Peritoneal Transport Data Before and After Peritoneal Rest in Patients with Prior and Recent Ultrafiltration Failure

		Recent UFF subgroup (n=20)		Prior UFF subgroup (n=15)		p
			p		p	
Cr-MTAC (mL/min)	Pre-PR	17±3.1	0.008	18.5±3.7	NS	NS
	Post-PR	14.1±4		17±5		NS
U-MTAC (mL/min)	Pre-PR	27.3±4	0.0001	26.5±5	NS	NS
	Post-PR	22.8±5		24.9±7.2		NS
UF (mL)	Pre-PR	384±176	0.0001	340±108	NS	NS
	Post-PR	653±180		512±330		NS
D/P Cr	Pre-PR	0.85±0.06	0.003	0.88±0.06	NS	NS
	Post-PR	0.80±0.07		0.86±0.08		NS

UFF = ultrafiltration failure; Cr-MTAC = mass transfer area coefficient creatinine; U-MTAC = mass transfer area coefficient urea; UF = ultrafiltration; D/P Cr = dialysate/plasma creatinine ratio; PR = peritoneal rest; NS = not significant.

Figure 2 — Evolution of peritoneal functional data before and after peritoneal rest in ultrafiltration failure patients, with and without a previous history of peritonitis. (A) Creatinine MTAC (mL/min), (B) Urea MTAC (mL/min), (C) D/P-Cr and (D) UF/4 h (mL). The *p* value in bold expresses the differences between groups in the comparison of the gradients. Posthoc analysis showed no statistically significant (*p*<0.05) differences in all the parameters evaluated when the 2 groups were compared. Cr-MTAC = mass transfer area coefficient creatinine; U-MTAC = mass transfer area coefficient urea; D/P Cr = dialysate/plasma creatinine ratio; UF/4h = ultrafiltration capacity; PR = peritoneal rest; NS = not significant.

we found that the response to PR in 20 patients with recently diagnosed UFF was the partial recovery of peritoneal transport and improved water and solute transport,

while patients with prior UFF for longer than 6 months showed a trend towards improvement; however, it was not statistically significant. This confirms that time is a main

factor in determining the reversibility of changes induced in UFF. The correlation of the morphological changes occurring in the human peritoneum chronically exposed to PD until the development of UFF and the time to PR could explain these differences. The anatomical substrate of UFF initially displays changes in the mesothelial cell phenotype (epithelial-mesenchymal transition), allowing these cells to acquire migration and extremely high vascular endothelial growth factor (VEGF) synthesis capabilities, with a final scenario characterized by submesothelial thickening and angiogenesis (20–22). Promptly interrupting the epithelial-mesenchymal transition process in mesothelial cells could stop and reverse the whole process. Peritoneal rest represents the discontinuation of continuous exposure to PD fluids responsible for these changes (22). The recovery of the epithelial phenotype by mesothelial cells and the regeneration of the submesothelial layer is a key factor in the complete recovery of the membrane. Enabling this recovery quickly could be the key to reversing peritoneal functional changes present in the first stages of UFF. At this stage, vascular endothelial growth factor causes vasodilation but probably does not yet induce capillary neoformation. When angiogenesis has been established, it is far less likely that any of these measures will be effective.

Our results also show that a previous history of peritonitis does not affect the response to PR. This strategy enabled patients to remain on PD for a mean time similar to the cohort of patients without UFF. This outcome suggests that PR could be an effective procedure for prolonging PD in patients with recently diagnosed UFF.

One of the limitations of our study is the long period of observation. Our group initially based the diagnosis of UFF empirically on clinical and functional data until criteria were established in 1998. There were changes in the quantification of UF over time, but with no differences in the procedure and the monitoring of peritoneal function over time. There were also a number of difficulties in establishing a proper control group under identical conditions, due to the impossibility of substituting PR for a real placebo. Comparing PR with the continuation of PD in similar situations makes no sense, from a clinical and ethical point of view, because continuing PD could lead to further glucose use and a worsening of the clinical situation.

We conclude that peritoneal rest leads to the partial or complete regression of a hyperpermeability state present in patients with UFF. When the same approach is applied for nontherapeutic reasons, peritoneal function remains unaltered. The response is independent of a previous history of peritonitis, and its early implementation is a major determinant of clinical results.

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