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SHORT REPORTS

Hospitalization Is Not Necessary for Peritoneal Dialysis Catheter Insertion

No scientific data exist to support inpatient peritoneal dialysis catheter insertion (PDCI). There is also no evidence to support that regular flushing of PDCs prior to PD training decreases the incidence of malfunction. Literature on these subjects is lacking. A brief, informal telephone survey that we performed across Canadian tertiary-care university hospitals prior to initiation of this study suggested that surgical PDCI in this country is generally performed as an inpatient procedure, and that there is no consensus on whether or on how often peritoneal catheter flushing is necessary prior to daily use.

As in most Canadian hospital centers, at our institution, hospital bed resources have become increasingly scarce, and in August 1999, the hospital administration demanded that PDCI be performed on an outpatient basis because the three hospital beds traditionally reserved for inpatient PDCI could no longer be secured. This study was therefore performed to compare the outcomes of inpatient versus outpatient PDCI.

The Moncrief PDC (1–3), which is generally inserted several months before use, does not get flushed prior to exteriorization and yet is reported to be highly functional. We therefore hypothesized that regular catheter flushing may not be necessary and this practice, previously performed weekly, was abandoned in August 1999, with initiation of outpatient PDCI.

PATIENTS AND METHODS

A total of 196 surgical PDCIs were performed at our institution between 1 August 1998 and 3 July 2000; 15 of these (7.6%) were repeat (second) procedures in a same patient. The center is a tertiary-care teaching hospital of the University of Manitoba and hosts the only PD program in the province, delivering care to 200 PD patients (± 10 over the past 2 – 3 years). Twenty-three percent of these patients are aboriginal; many reside on reserves, remote from any city or large town. Chart reviews of 106 patients that had inpatient PDCI (and weekly catheter flushes until training commenced; group A) between 1 August 1998 and 31 July 1999 were performed from the date of PDCI until 3 months post insertion. Ninety patients that had outpatient PDCI (without flushes; group B) from 1 August 1999 to 3 July 2000 were prospectively followed for 3 months from the date of PDCI.

Swan-neck Missouri catheters were inserted in all cases by the same experienced surgeon. All patients were routinely given cefazolin 1 g intravenously 1 hour before surgery (unless allergic to cephalosporins, in which case vancomycin was administered); preoperative intramuscular opiate analgesic was administered. Patients were noninvasively monitored; they were prepped and draped in the supine position, and the area of insertion (lateral entry) infiltrated with 0.5% lidocaine without epinephrine. Skin and anterior rectus sheath incisions were made and a purse-string suture at the posterior rectus sheath was placed, with its subsequent incision and PDCI into the pelvis using a director. A purse-string suture was then tied at the junction of the Silastic ball and the Dacron cuff, and the catheter tunneled, using a trocar, at a predetermined exit site. After demonstration of good inflow and outflow of dialysate fluid and absence of fluid leak, the wound was closed. In the recovery area, the catheter was again flushed twice with 0.5 L 1.5% dextrose dialysate containing heparin 500 U.

For inpatient PDCI (group A), patients were admitted directly to a dedicated medical ward where all nursing staff are trained and experienced in performing PD and in caring for postoperative PDCI patients. The patients were monitored in hospital for 48 hours. Outpatient PDCI patients (group B) presented for their procedure to the day surgery department in the early morning; after PDCI, they were observed in a recovery area for 4 – 6 hours by the same nurses. Any of these patients residing out of town, requiring more than one half hour travel, were asked to make arrangements to remain in the city overnight and to proceed home the following morning if no problems occurred. All patients were prescribed stool softeners and laxatives on discharge.

Those patients that had inpatient PDCI returned to the PD unit weekly for catheter flush with 1 L 1.5% dextrose dialysate with heparin 1000 U, and exit-site dressing change, until commencement of training. Those patients that had outpatient PDCI returned

weekly just for the exit-site dressing change and had the catheter flushed only, approximately, 1 week prior to commencement of training to ascertain its function. All patients with a nondraining catheter were given an aggressive 24-hour course of laxatives to try to restore catheter function. All patients initiated PD training within 4 weeks of catheter insertion.

For each group, patient demographics, underlying primary end-stage renal disease diagnosis, incidence of exit-site infections (ESI), peritonitis, catheter malfunction (defined as inability to fill or drain), and dialysate leak were recorded. For those patients that had outpatient PDCI, any emergency room or dialysis unit visit within 24 hours of discharge was also documented.

Data were analyzed using two-tailed (Fisher's) exact test for proportions, and t-test for continuous variables.

RESULTS

The two groups were similar in age, incidence of diabetes mellitus, and whether they had been receiving chronic hemodialysis or were conservative predialysis patients prior to PDCI. The male-to-female ratio and weight were different between the two groups (Table 1). Incidence of complications for group A versus group B were, respectively, ESI 16.98% (n = 18) versus 17.78% (n = 16); peritonitis 8.49% (n = 9) versus 12.22% (n = 11); catheter malfunction (which consisted of no drainage in all cases) 17.92% (n = 19) versus 22.22% (n = 20); catheter removal 11.32% (n = 12) versus 5.55% (n = 5); dialysate leak 1.89% (n = 2) versus 2.22% (n = 2). There was no statistically significant difference in incidence of any complication between groups (Table 2).

Of those patients that had outpatient PDCI, 6 (6.7%) returned to the emergency room or dialysis unit within 24 hours of discharge: 4 for bleeding at the incision, 1 with dialysate leak, 1 with transient fever and chills. All episodes were self-limited and no patient required admission.

TABLE 1
Patient Demographics

	Group A[a] (n=106)	Group B[b] (n=90)	p Value
Sex (M/F)	66/40	38/52	0.006
Age (years)	51.1±17.2	54.3±14.5	0.17
Weight (kg)	77.0±18.6	71.3±15.9	0.04
Diabetes mellitus	42	41	0.47
Hemodialysis	57	44	0.57
Conservative	49	46	

[a] Peritoneal dialysis catheters inserted on an inpatient basis; weekly catheter flushes until training commenced.
[b] Peritoneal dialysis catheters inserted on an outpatient basis; no flushing.

TABLE 2
Results

	Group A[a] (n=106)	Group B[b] (n=90)	p Value
Exit-site infection	16.98% (18)	17.78% (16)	1.0
Peritonitis	8.49% (9)	12.22% (11)	0.48
Malfunction	17.92% (19)	22.22% (20)	0.48
Removal	11.32% (12)	5.55% (5)	0.20
Leak	1.89% (2)	2.22% (2)	1.0

[a] Peritoneal dialysis catheters inserted on an inpatient basis; weekly catheter flushes until training commenced.
[b] Peritoneal dialysis catheters inserted on an outpatient basis; no flushing.

DISCUSSION

Health-care resources are becoming increasingly taxed in an era when countries are having to cut budgets for health-care delivery, despite a rising need. In Canada, where "hallway medicine" for patients awaiting a hospital bed (often for days) from the emergency room has become a national norm, this lack of resources is obvious. At our institution, the site of the only but very large provincial PD program, consisting of more than 200 patients, PDCI had to become an outpatient procedure to try to alleviate the very high demand for hospital beds.

Traditionally, PDCI has been an inpatient procedure for the majority of Canadian patients. Until now, there have been no studies of clinical outcomes of outpatient versus inpatient PDCI. Our findings suggest that outpatient PDCI is safe. No difference in complication rate was noted compared to inpatient insertions. The reported incidence of early (within 2 weeks of insertion) peritonitis is not well established but was noted to be 12.5% in one study (4). Reported early catheter malfunction has been extremely variable, between 0% and 20% (5–9), as has an incidence of dialysate leak between 2% and 24% (5–8,10,11), depending on implantation technique, catheter employed, and reporting center. The incidence of early ESI is even more obscure given an extreme lack of literature on this topic. Our complication rates are within these ranges despite the fact that they reflect 3-month patient follow-up post catheter insertion. Group A and group B patients had statistically significantly more males and more females, respectively, and group A patients had a higher weight compared to group B, but there exist no data to suggest that these differences should affect outcome with PDCI.

This study also demonstrates the safety of outpatient PDCI, despite the population having a significantly high number of remote rural inhabitants, not infrequently in settings with less than optimal conditions for performing PD. Furthermore, our results show that there is no apparent advantage to routine catheter flushing.

We therefore conclude that outpatient PDCI should be instituted so that hospitalization resources can be allocated to patients that require them, and to reduce costs. We also conclude that routine catheter flushing, outside the intraoperative and immediate postoperative setting, is not necessary and should not be performed.

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Placement of Peritoneal Dialysis Catheters on an Outpatient Basis

Health-care costs for the growing end-stage renal disease (ESRD) population are projected to increase dramatically, with Medicare costs for ESRD in the United States rising from $5 billion to $12 billion between 1992 and 1998 (1). A recent study at our institution analyzed expenses accrued by dialysis patients and determined that hospitalization contributed substantially to the cost of dialysis (2). Reducing unnecessary admissions may lead to great savings.

Protocols for peritoneal dialysis (PD) catheter placement vary. Many nephrologists admit patients for PD catheter placement; however, to minimize costs, same-day surgery units are used extensively to avoid admission following many minor surgical procedures. This paper reports a 10-year experience of outpatient catheter placement at a single institution, evaluating surgical and early catheter-related complications occurring during the first postoperative week. The purpose of this study was to examine the safety of outpatient catheter placement.

MATERIAL AND METHODS

Electronic and paper medical records were retrospectively reviewed for all patients in the University of Pittsburgh Peritoneal Dialysis Registry. Patients that had catheters placed from 1 January 1992 to 1 January 2002 were included in the study. All patients signed a consent form permitting review and publication of patient data, in a protocol approved by the University of Pittsburgh Institutional Review Board for Human Use. All catheters analyzed were double-cuffed Tenckhoff catheters; four investigational catheter types were excluded from the analysis. All catheters were placed by surgeons, usually with local anesthesia and intravenous sedation. Most

catheters were placed using a paramedian incision, with the deep cuff fixed to the peritoneum by purse-string suture. One prophylactic dose of either cephalosporin or vancomycin was given intravenously immediately preoperatively. Three quick in-and-out flushes (1 L each) with 1.5% dextrose dialysate containing heparin 500 U/L were performed by a dialysis nurse during the immediate postoperative period. Peritoneal dialysis training was deferred for 7 to 14 days after catheter insertion, although outpatient PD using low volumes was initiated before home training in a few patients. A nurse trained in dialysis performed sterile exit-site care weekly until training began. Patients were instructed not to shower or tub bathe and to keep a sterile dressing in place until the exit site was well healed; usually this was 10 to 14 days. A protocol to prevent *Staphylococcus aureus* exit-site infection (either exit-site mupirocin or oral rifampin) was initiated when training began.

Early catheter-related complications were recorded, as well as emergency department visits and admissions for catheter-related problems within the first 7 days after surgery. A 1-week follow-up was selected to capture all potential complications that may have been related to surgical or postoperative catheter care. Any patient treated in the emergency department and subsequently admitted was counted once as an admission. If a catheter was replaced, the second catheter was considered a separate event.

Data are expressed as proportions and mean values with standard deviation, or median values with range, where appropriate. Proportions were compared using chi-square. Continuous variables were compared using two-sample t-test or Mann–Whitney U test, depending upon distribution. Catheter survival was determined using the Kaplan–Meier method, censoring for death, transplant, and transfer to hemodialysis. Comorbidity for each patient was determined using the Charlson Comorbidity Index (CCI), a validated method that includes age and diabetes mellitus.

RESULTS

During the decade studied, 251 Tenckhoff catheters were inserted into 225 patients. Eighty-six PD catheters were placed during a hospital admission. The majority of these catheters were placed during admission due to late referral and the need to immediately start renal replacement therapy (33%), or during admission for other medical reasons (31%), or during admission for renal transplant failure (22%). Only 6% were admitted solely for PD catheter insertion, and another 6% were admitted for catheter replacement due to either peritonitis or catheter malfunction. Patients admitted for catheter placement were similar in age (51 ± 19 years vs 48 ± 15 years), gender (both 54% women), race (84% vs 85% Caucasian), and presence of diabetes mellitus (39% vs 33%) to patients having outpatient catheter placement, but had more comorbidity (median CCI 6 vs 4, $p < 0.001$) and lower serum albumin at the start of PD (median 3.5 g/dL vs 3.7 g/dL, $p = 0.002$).

Same-day surgery was utilized for the insertion of 165 PD catheters in 143 patients, representing 65% of all PD catheters inserted during the decade studied. There were 18 catheter-related complications during the first 7 days after outpatient catheter insertion, most of which were minor and easily managed. Leaking of dialysate at the exit site occurred six times; all resolved. Another six complications were related to constipation, vomiting, and/or abdominal pain, which in two cases led to malposition of the catheter. Only 2 patients developed a PD-related infection during the postoperative week; both were successfully treated as outpatients. Four patients with catheter-related complications required admission (2.4%) during the first week after placement. An additional four emergency department visits did not require admission (2.4%).

Only two catheters (1%) were removed during the 7 postoperative days. One patient developed a delusional medication side effect causing him to pull out his own catheter; the catheter was replaced during admission. A second catheter was removed due to poor drainage. Catheter survival with same-day-surgery catheter placement was 84% at 1 year, as shown in Figure 1.

DISCUSSION

The present study suggests that PD catheters can be safely placed on an outpatient basis in at least two thirds of patients. Complications were infrequent, minor, and easily resolved, with only 1% of catheters lost during the first week post placement in outpa-

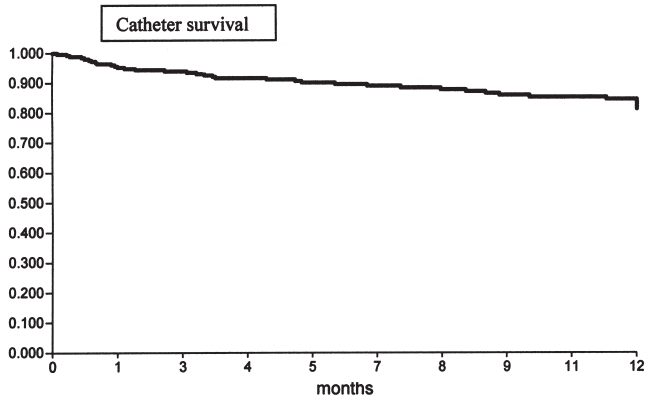

Figure 1 — One-year catheter survival of peritoneal dialysis catheters placed on an outpatient basis.

tients. Support for this approach comes from a recent study of 3152 patients undergoing same-day surgery for various procedures (3). Only 5% of the cases required unanticipated admission; our results (2.4% admitted postoperatively) compare favorably. The 1-year catheter survival rate for catheters placed in the outpatient setting was excellent. Outpatient placement of catheters will result in considerable cost savings and is a safe approach in most patients.

Subsequent emergency visits and admissions were uncommon after outpatient catheter placement. In our study, 4 patients required hospitalization during the first week, 2 with abdominal pain and constipation occurring in the immediate postoperative period (< 7 days). An additional 4 patients visited the emergency department (primarily for vomiting) but did not require admission. Gastrointestinal complaints, both constipation and nausea, are common in this population and are not likely to be diminished by admitting the patient to place the catheter. Instead, close attention to the bowel regimen of patients receiving PD catheters is important, especially since most patients require mild narcotics to control pain, which may exacerbate constipation and nausea. An oral antiemetic as well as a narcotic and laxatives for home use may help the patient postoperatively, and minimize the risk of gastrointestinal complications.

Catheter complications occurring during the first 7 days after placement were either mechanical in nature or infectious, but both were infrequent. In our study, early dialysis leaks occurred in 3% of catheters, less than in the literature (7% – 8%) (4–6). These leaks were at the exit site and usually were related to flushing of the catheter with 1-L volumes immediately postoperatively. This approach has recently been abandoned as unnecessary for catheter patency. Infectious complications during the postoperative period were uncommon in our patients, with only one exit-site infection and one peritonitis episode, both successfully treated. This low rate can be attributed to the prophylactic antibiotics given at the time of surgery, as well as to management of the sterile dressing until the exit site was well healed.

There are several advantages to outpatient placement of PD catheters. Cost savings from outpatient placement of catheters are considerable. At our institution, an average hospital room costs $1046 per day. Hospitalization is also more disruptive than an outpatient procedure to the patient's life. Furthermore, admission exposes the patient to the potential of colonization with hospital-acquired resistant organisms such as vancomycin-resistant enterococcus or methicillin-resistant staphylococcus.

This study identifies common reasons patients sought medical attention after catheter placement, which may help improve postoperative care and reduce subsequent emergency visits and hospitalization. Patients should be sent home with medications to control nausea and pain, receive a perioperative bowel regimen to prevent constipation, and be instructed to keep their sterile dressing dry and intact. Same-day catheter placement will result in lower patient care costs. We conclude that, in most patients, PD catheters can be safely placed on an outpatient basis and that this is the preferred approach.

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A Novel Salvage Technique That Does Not Require Catheter Removal for Exit-Site Infection

The advent of peritoneal dialysis (PD) therapy produced a significant improvement in the care of patients with chronic renal failure. The major complication of PD is peritonitis. However, recent

advances in connect systems (ultraviolet sterilization systems and heated plate system) for PD bag exchanges have reduced transcatheter peritonitis. However, catheter loss due to intractable exit-site or tunnel infection remains a significant problem in maintaining PD. In addition, these infections are an important cause of patient withdrawal from PD therapy and prevent some increase in the number of PD patients.

Kidney transplantation is very rare in Japan compared to Western countries; most patients undergo long-term blood purification therapy such as hemodialysis and PD. It is therefore apparent that long-term maintenance of the Tenckhoff catheter as peritoneal access is critically important in patients undergoing PD.

Exit-site and tunnel infections are difficult to cure and, if persistent, may necessitate the removal of an otherwise well-functioning catheter.

Prior to 1995, we utilized the "unroofing method" (1,2) to treat such patients with persistent infection. However, several years ago we adopted a novel salvage technique for treating intractable exit-site and tunnel infections that involves the use of a titanium extender (Accurate Surgical Instruments, Toronto, Ontario, Canada) to facilitate translocation of the PD exit-site. We describe here this technique and report our clinical experience to date.

MATERIAL AND METHODS

Twenty-two patients undergoing maintenance PD at Yamanashi Medical University and Kameda General Hospital were enrolled. All catheters used at initial insertion were swan-neck type abdominal catheters, JB-6, JB-5, or JB-5(a) (Accurate Surgical Instruments). These patients exhibited catheter exit-site infection, suspected to be limited to the outer cuff, and symptoms that did not respond to adequate systemic antibiotic therapy and frequent sterilization of the exit site with povidone–iodine. Prior to 1994 we used the unroofing method and cuff shaving. However, after 1995, all such patients underwent the exit-site translocation technique.

Sufficient information regarding each potential therapy (*i.e.*, conventional "unroofing and cuff resection," catheter exchange, and this technique) was provided to the patients and full informed consent was obtained.

Translocation of the PD exit site using a titanium extender was performed under spinal anesthesia. The exit site was brushed with povidone–iodine soap and the PD catheter tunnel was irrigated [Figure 1(a)]. The PD exit site was first incised in a spindle shape and a further incision was made right above the outer cuff and the catheter [Figure 1(b)]. The tissue around the catheter was resected together with the catheter in order to expose the outer cuff to the skin [Figures 1(c,d)] and to prevent infections. The outer cuff and the extraperitoneal part of the catheter were dissected and removed, with the infected tissue, leaving the intraperitoneal part untouched with its inner cuff as well as a short segment of the extraperitoneal portion [Figures 1(c,d,e)]. It is necessary to verify whether the infected region extends beyond the region of the outer cuff. If it does, this salvage technique must be abandoned; if it does not, a new extraperitoneal catheter is connected to the remaining part of the old catheter after careful resterilization of the old tunnel [Figure 1(f)]. We use the titanium extender to connect both catheters. It is not necessary to use silicone glue or other adhesive material. Double suturing with 2-0 nylon sutures to each side of the titanium extender prevents slippage [Figure 1(g)]. A new exit site was then made using the tunneler, and the titanium extender was fixed to the abdominal wall fascia [Figure 1(h)] with nylon thread in such a way that the extender is not excessively bent.

The entire infected wound was removed using an electrosurgical knife and sufficiently sterilized. An absorbent monofilament thread was used to repair the subcutaneous tissue and the skin was sutured [Figure 1(i)].

Postoperative treatment is povidone–iodine sterilization to the exit site twice daily, with oral antibiotics for 2 weeks.

RESULTS

This salvage technique was performed 22 times in 22 patients between April 1995 and December 1998. Bacteria recovered from exit sites included *Pseudomonas aeruginosa* (n = 4), methicillin-resistant *Staphylococcus aureus* (MRSA; n = 3), methicillin-sensitive *S. aureus* (MSSA; n = 9), and other bacteria (n = 6).

Only 1 patient developed a recurrent tunnel infection with the same strain of organism (*P. aeruginosa*, after a period of 4 months). The remaining 21 patients did not develop any recurrence of infection by the sixth postoperative month. The new exit sites and wounds were completely healed by the 10th postoperative day.

DISCUSSION

Persistent exit-site and tunnel infections are an important problem and are hazards to patients maintained on PD therapy. Until recently, these intractable infections forced either the removal of an otherwise well-functioning catheter (3) or the use of the unroofing method (1,2).

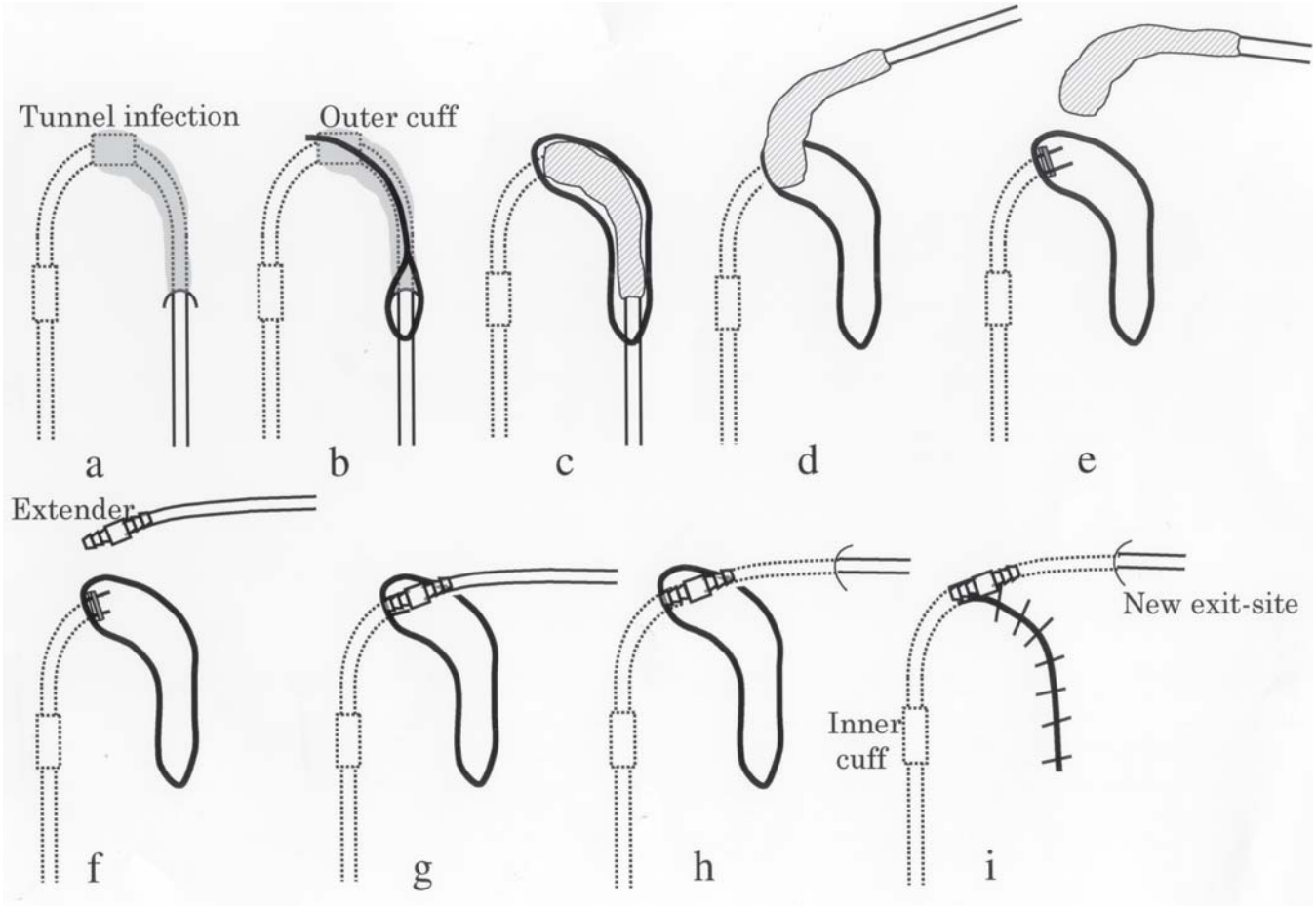

Figure 1 — A salvage technique for peritoneal dialysis catheter with exit-site/tunnel infection, using the titanium extender. A tunnel infection extending to the outer cuff (a). A skin incision is made right above the catheter (b); the tissue around the catheter and the catheter are resected together (c,d); clamp; the central portion of the outer cuff is cut off (e); titanium extender is attached to the catheter (f,g); new exit site is made (i).

There have recently been reports regarding translocation of the PD exit site using a connector for the hemodialysis outer shunt (4), a presternal catheter and extender (5,6), or using a Peri-Patch Repair Kit (Quinton Instrument, Seattle, Washington, USA) (7,8).

Advantages of catheter translocation for the treatment of exit-site infections are as follows. First, in the unroofing method, a new exit-site infection often requires catheter removal, since the distance from the skin to the inner cuff or the insertion site on the peritoneum is very short. However, after translocation of the PD exit site, the incidence of exit-site infection is comparable to that following the catheter exchange method, since sufficient distance from the skin to the inner cuff is obtained. Second, there is no leakage of dialysate since no operation on the site of insertion at the peritoneum is required.

There are several advantages to using the titanium extender for the repair and translocation of the PD exit site. First, the titanium extender is approved by the Japanese government for the repair of PD catheters; it undergoes less degradation over time and, therefore, has prolonged *in vivo* stability. Second, since the package includes a silicon catheter (15 cm long), other catheters are not required, thereby resulting in a cost reduction. Third, there is no requirement for Dacron fibers and this reduces the chance of infection. Fourth, titanium is safe to insert into the body since organic solvents, *etc.*, are not used. Fifth, bending and slippage at the connection site are prevented since the titanium extender itself is fixed to the fascia.

There are some problems with the technique of translocation of the PD exit site: the operation is performed over an infected wound area and there is a risk of iatrogenic peritonitis by contaminating the catheter. However, none of our patients developed leukocytosis in the dialysate or overt peritonitis, despite the fact that we did not administer antibiotics into the peritoneal cavity. Therefore, the strict attention that was given to the eradication of infection during the operation resulted in subsequent infection not

being a major problem. Although no macroscopic infection may be evident extending from the outer cuff to the inner cuff, there is the possibility of transcatheter peritonitis or recurrent tunnel infection occurring. Extreme caution should be taken in cases involving *P. aeruginosa*, which is associated with major production of biofilm. In one case, we experienced early recurrence of tunnel infection with *P. aeruginosa*. We observed extension of the infection from the outer cuff to the central side during the surgical operation, but considered that sufficient sterilization had been performed. Ultimately, pus discharge occurred 4 months later and the catheter was removed. After this case, we changed our protocol such that the catheter-exchange method was performed in any case suspected of having extended infection, especially involving *P. aeruginosa*. Last, local tissue reaction with titanium material is not known and it is unlikely that an inflammatory reaction may be induced, although this is a possibility.

This technique can be performed in cases of persistent exit-site infection or tunnel infection limited to the outer cuff, without the discontinuation of PD therapy. We believe this technique is useful and efficacious in such problematic patients.

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Soluble Transferrin Receptor Is Not a Reliable Marker of Iron Deficiency in Pediatric CAPD Patients

Successful anemia therapy in patients with chronic renal failure (CRF) treated with recombinant human erythropoietin (rHuEPO) requires adequate available iron to keep up with the demands of erythropoiesis. To fulfill this task, body iron status must be closely monitored (1,2). Unfortunately, no single test or combination of tests allows discrimination of iron deficiency with complete confidence in CRF (1,3). Although the most frequently used markers for monitoring iron status are serum ferritin and transferrin saturation (TS) (2), there are some limitations in the diagnostic value of these markers for iron deficiency in uremic subjects. Occult inflammation, often present in patients with CRF, results in increased serum ferritin without a change in iron status (1,3). The tendency for iron to be sequestered in the storage pool and reticuloendothelial blockade in CRF patients is another important drawback of measuring serum ferritin (1,2). Concentrations of serum iron and total iron binding capacity (TIBC) are known to decrease in the presence of acute-phase reaction and to show inter- and intrapatient variability (1,3). In addition, TIBC is known to decrease independently of iron status, due to malnutrition (1). Hence, the inaccuracy of these routine tests has compelled investigators to search for new alternative methods to better define iron de-

ficiency, as well as iron availability, in uremic individuals. For these reasons, during the past few years, the validity of measuring soluble transferrin receptor (sTfR) has been tested in some reports. Although it is accepted as a reliable marker in nonuremic anemic individuals, there is not enough experience in uremic individuals (1,4,5).

In iron deficient states, cells increase their production of cellular transferrin receptor (TfR), which binds to transferrin and leads to internalization of iron. Since serum level of truncated cellular TfR is proportional to cellular receptor expression, cellular and soluble TfR levels are expected to increase in iron deficiency (1). It has been indicated that levels of sTfR correlate directly with erythropoiesis, and inversely with the amount of iron available for erythropoiesis (6–8). Therefore, the major advantage of sTfR measurement over standard hematologic parameters appears to be the specificity of its response to changes in iron status and erythropoiesis, without being influenced by chronic inflammatory states (7).

Data for assessing iron status in both adult and pediatric continuous ambulatory peritoneal dialysis (CAPD) patients are limited, and the reliability of routinely used diagnostic tests is a matter of controversy (9,10). The present study was designed to assess iron status in anemic pediatric CAPD patients and to compare the value of sTfR measurement with other standard hematologic parameters in the diagnosis of iron deficiency.

PATIENTS AND METHODS

Twenty (12 females, 8 males) CAPD patients and 15 (9 females, 6 males) healthy age- and sex-matched controls were enrolled in this study. Underlying renal disorders were as follows: reflux nephropathy in 3 patients, chronic pyelonephritis in 2, membranoproliferative glomerulonephritis in 2, cystinosis in 2, infravesical obstruction in 1, neuropathic bladder in 1, hypoplastic/dysplastic kidneys in 1, crescentic glomerulonephritis in 1, hemolytic uremic syndrome in 1, focal segmental glomerulosclerosis in 1, Alport's syndrome in 1, amyloidosis in 1, juvenile nephronophthisis in 1, and unknown causes in 2. None of the CAPD patients were supplemented with iron or rHuEPO. There was no history of blood transfusion within the previous 10 weeks. No patient was vitamin B_{12} or folate deficient, and no patient was receiving aluminum-containing phosphate binders. Descriptive features of the patients are summarized in Table 1.

Complete blood count, serum iron profile, serum ferritin, and sTfR were studied. Serum ferritin was assayed using a chemiluminescence technique (Immulite 2000 Euro/DPC Ltd, Gwynedd, UK). The concentration of sTfR was determined using an ELISA that uses monoclonal antibodies (R&D Systems, Minneapolis, Minnesota, USA). All samples were studied in duplicate. The reference range of the commercial kit for sTfR for normal subjects is 8.7 – 28.1 nmol/L.

Hematologic parameters, intact parathormone levels (PTH), and serum protein and albumin levels were also measured. In addition, residual urine output (mL/kg/hour) and weekly urea clearances (Kt/V urea) were calculated. Serum erythropoietin (EPO) levels were measured in 15 of 20 patients using ELISA (EPO-ELISA Medac; Geschäftseinheit Diagnostik, Hamburg, Germany). The reference range of the EPO ELISA kit for normal individuals is 4 – 25 mIU/mL.

Since iron deficiency occurs at higher TS and serum ferritin levels in uremic patients than in the general population, in this study, a serum ferritin level < 150 ng/mL and TS < 21% were considered indicative of iron deficiency, as indicated in previous publications (1,2).

Pearson's and Spearman's correlation coefficients, Student's t-test, and Mann–Whitney U and multiple regression analysis were used for the statistical analysis. Associations between variables were evaluated using the method of least squares. Multiple linear regression analysis was used to assess the relationship between sTfR and other outcome parameters such as dialysis adequacy, PTH, and serum albumin levels. Results are mean ± SD.

RESULTS

Mean age was 12.7 ± 2.7 (7 – 19) years in the CAPD group and 11.6 ± 0.8 years in the control subjects ($p > 0.05$). Mean standard deviation score for height (height SDS) was −2.7 ± 1.6, and weight SDS was −1.9 ± 0.9 in the CAPD patients, indicating growth retardation and probably malnutrition. Mean duration of CAPD was 17.8 ± 10 months (Table 1). Mean values for hemoglobin and hematocrit were significantly lower in CAPD patients compared to those in healthy controls (6.3 ± 1.3 g/dL and 19.8% ± 3.7% vs 13.7 ± 0.8 g/dL and 39.1% ± 2.3%, $p < 0.001$) (Table 2).

Neither serum iron profile (serum iron 92 ± 27 µg/dL, TIBC 357 ± 89.8 µg/dL, and TS 27.3% ± 10.8%) nor serum ferritin levels (313 ± 430 ng/mL) suggested iron deficiency, according to the mean values obtained. Although significantly lower sTfR levels were detected in the CAPD group compared to the control group (12.4 ± 5.2 nmol/L vs 22.9 ± 5.0 nmol/L, respectively, $p < 0.001$), mean concentrations of sTfR for both groups were within the normal reference values of the commercial kit (Table 2). None of the patients had elevated sTfR levels; 7 (35%)

TABLE 1
Descriptive Features of the Patients

	Normal range	Mean±SD	Range
Age (years)		12.7±2.7	7–19
Body weight (kg)		31.1±12.4	13–55
Height (cm)		134±19	100–164
Weight SDS		−1.9±0.9	−3.5–0.48
Height SDS		−2.7±−1.6	−6.1 to −0.4
Vitamin B_{12} (pg/mL)	160–970	646±257	404–1300
Folate (ng/mL)	1.5–16.9	37.3±21.9	10–96
Protein (g/dL)	6.4–8.1	5.8±0.8	4.6–7.6
Albumin (g/dL)	4.0–5.3	3.3±0.6	2–4.7
Intact PTH (pg/mL)	12–72	519±432	7–1455
Duration of dialysis (months)		17.8±10	2–39
Urine output (mL/kg/hour)		0.85±0.22[a]	0–3.8
Kt/V urea[b]		1.85±0.7	0.7–3.5

SDS = standard deviation score; PTH = parathormone.
[a] Mean ± standard error of the mean.
[b] Weekly urea clearance.

TABLE 2
Complete Blood Count and Serum Transferrin Receptor (sTfR) Levels in 20 Pediatric CAPD Patients and 15 Healthy Age- and Sex-Matched Controls

	Normal range	CAPD	Control	*p* Value
Hb (g/dL)	12–16	6.3±1.3	13.7±0.8	<0.001
Hct (%)	36–46	19.8±3.7	39.1±2.3	<0.001
MCV (fL)	78–98	88±3	83±0.7	<0.001
RDW (%)	<14.5	13.7±1.4	11.9±0.5	<0.001
sTfR (nmol/L)	8.7–28.1	12.4±5.2	22.9±5.0	<0.001

MCV = mean cell volume; RDW = red cell distribution width.

had sTfR concentrations less than the lower limit of normal for the commercial kit (< 8.7 nmol/L).

Despite the fact that mean values of TS and ferritin did not indicate iron deficiency in our CAPD patients, 12 of 20 patients (60%) had ferritin levels < 150 ng/mL and/or TS < 21%, which is consistent with iron deficiency. However, levels of sTfR (14.4 ± 5.37 nmol/L) were lower than anticipated, irrespective of the severity of the anemia. Mean serum EPO levels in the anemic CAPD patients (15 of 20 patients) were also found to be within the normal limits (7.99 ± 5.88 mIU/mL, range 2.4 – 20.1 mIU/mL, median 4.9 mIU/mL).

Lower sTfR levels were obtained in 6 of 20 patients, all of who had serum ferritin concentrations above 300 ng/mL (mean 863 ± 422 ng/mL), compared to the levels in the remaining 14, all of who had serum ferritin below 300 ng/mL (8.91 ± 3.2 nmol/L vs 13.86 ± 5.2 nmol/L, respectively, $p < 0.05$). Moreover, a highly significant inverse correlation was observed between serum ferritin and sTfR levels ($r_s = -0.61$, $p < 0.05$) in those 6 patients.

There were no correlations between concentrations of sTfR and Hb, Hct, TS, and serum ferritin levels, but there was a weak positive correlation between sTfR levels and TIBC ($p < 0.05$, $r = 0.476$). There was also no correlation between TS and serum ferritin.

Serum protein and albumin levels were also measured in the two groups. In the CAPD group, protein and albumin levels were found to be significantly lower than those in the control group (5.8 ± 0.8 g/dL vs 7.5 ± 0.4 g/dL, and 3.3 ± 0.6 g/dL vs 4.7 ± 0.8 g/dL, respectively, $p < 0.001$). There were no correlations between protein/albumin and sTfR levels in either of the two groups. Intact PTH levels (mean 519 ± 432 pg/mL, normal range 12 – 72 pg/mL) in the CAPD patients indicated secondary hyperparathyroidism. Kt/V urea was also calculated and found to be 1.85 ± 0.7. Potential effects of intact PTH, serum albumin, and Kt/V urea levels on sTfR concentrations were also evaluated using multiple regression analysis. Serum sTfR levels were slightly influenced by PTH levels ($p = 0.056$), but not necessarily by other outcome factors.

DISCUSSION

There are no clear data indicating which tests are the most valid in the diagnosis of iron deficiency in uremic patients, and accurate definition of iron deficiency presents some difficulties (1,2). In 1989, TfR was stated to be a novel index of early tissue iron deficiency in normal individuals by demonstrating strong correlations between TfR and standard iron

parameters (6). Its soluble truncated form, sTfR, has also been recommended as a reliable index in the detection of iron deficiency, even when iron storage is maintained at normal levels in adult uremic patients (11). In 1998, Tonbul *et al.* emphasized the validity of sTfR in the diagnosis of iron deficiency in adult hemodialysis patients (4). It was also well documented that sTfR is not only an early marker of tissue iron deficiency, but also a useful indicator of rHuEPO response and treatment failure in both adult and pediatric dialysis patients (9,12). In contrast to those reports, Baldus *et al.* evaluated iron status in 95 adult uremic patients, with or without rHuEPO therapy, using different tests, including serum iron profile, serum ferritin, sTfR, and zinc protoporphyrin levels. Although they showed a weak correlation between sTfR and Zi-protoporphyrin levels, the authors stressed the inconsistent results with different assays and could not recommend any of these tests as explicitly reliable (13).

We scrutinized previously published studies that determined whether sTfR is useful in the assessment of iron stores in pediatric peritoneal dialysis patients. Daschner *et al.* evaluated the clinical usefulness of sTfR in 27 pediatric dialysis (11 hemodialysis, 16 peritoneal dialysis) patients receiving rHuEPO therapy (10). They demonstrated that sTfR is a sensitive indicator of individual rHuEPO responsiveness in pediatric patients, finding a positive correlation between sTfR and weekly rHuEPO dose and a negative correlation between sTfR and rHuEPO efficacy index (rHuEPO dose divided by Hb concentration) (10). That is the only published report on sTfR in pediatric dialysis patients so far.

In our study, CAPD patients had significantly lower sTfR levels compared to controls. Although speculative, our data indicate that nonelevated sTfR levels in our anemic CAPD patients represent hypoproliferative erythropoiesis due to defective endogen EPO production, whereas normal sTfR levels in healthy controls represents normal erythropoiesis, as previously reported by Beguin *et al.* (5). Consistent with this claim, endogen EPO levels were found to be within the normal limits in our severely anemic CAPD patients. It is well known that serum EPO levels are significantly elevated parallel to the severity of anemia in nonuremic individuals. However, despite severe anemia, mean serum concentrations of EPO (7.99 ± 5.88 mIU/mL) in our uremic patient population were found to be inappropriately low, a condition that could be named relative EPO deficiency.

Although iron deficiency was defined, using standard hematologic parameters, in 12 of 20 patients, their sTfR levels were markedly lower than those in the controls. Therefore, along with relative EPO deficiency, it was necessary to investigate if there could be other factors that negatively affect sTfR levels. Considering sTfR is a plasma protein, we wanted to examine whether poor nutritional status of CAPD patients would have a negative effect on blood concentration of sTfR. In the CAPD group, neither a weight SDS suggesting undernutrition, nor total protein and albumin levels (found to be significantly decreased compared to those in the controls) correlated with sTfR levels. In 1996, Kuvibidila *et al.* determined the influence of undernutrition on sTfR concentrations in 99 Zairean women and reported that undernutrition did not significantly affect sTfR concentrations (14). It should be highlighted that one of the major limitations of this study is the small number of patients. In addition, the presence of occult inflammation in this patient group resulted in not only misinterpretation of the hematologic parameters used to evaluate body iron status, but also its effect on the status of nutrition and the well-being of the patients.

A possible explanation for the decreased sTfR concentrations in our CAPD patients could be the presence of iron overload. This hypothesis was tested by Khumalo *et al.* in 1998 in 150 subjects from rural Zimbabwe. The authors suggested that sTfR is decreased in subjects having iron overload (15). In our study, we detected moderately lower sTfR concentrations in 6 CAPD patients that had elevated serum ferritin levels (863 ± 422 ng/mL) than those that did not have elevated serum ferritin levels. Although an elevated ferritin level was thought to be attributable mainly to chronic occult inflammation in these patients, previous blood transfusions may also have played a role. The lack of elevated levels of sTfR in our patients, despite the presence of iron deficiency in at least half of them, could be due to its impaired synthesis due to relative EPO deficiency secondary to renal failure, or to a suppressive effect of iron overload on erythropoiesis. As there are not sufficient data, further investigations are needed to clarify these matters.

In conclusion, in this study, diverse and conflicting results were obtained in evaluating all parameters used for determining iron deficiency, including serum iron, TS, serum ferritin, and sTfR. None of these markers correlated with each other, except sTfR and TIBC. Although standard parameters indicated iron deficiency in 12 of 20 patients, we failed to observe the expected elevations in sTfR concentrations. Thus, testing sTfR levels seems to have no benefit over other standard hematologic parameters for the diagnosis of iron deficiency in pediatric CAPD patients. Therefore, sTfR should not be considered a reliable marker for the diagnosis of iron deficiency, but rather a valuable novel marker of erythropoietic activity. In patients on rHuEPO, sTfR can be used with a great validity as a follow-up index for erythropoietic activity. It can be speculated that, if sTfR measurement is

accompanied by serum iron profile and ferritin levels to detect iron deficiency, sTfR might provide complementary information about body iron status.

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Lymphocyte Subset Counts in CAPD Patients in Relation to Administration of Recombinant Human Erythropoietin and Angiotensin-Converting Enzyme Inhibitors

A decrease in total lymphocyte count (TLC) during the course of continuous ambulatory peritoneal dialysis (CAPD) is an indicator of disturbances in immune response and nutritional status, and is a prognostic index of mortality in CAPD patients. In the present study, we attempted to determine whether recombinant human erythropoietin (rHuEPO) and/or angiotensin-converting enzyme inhibitors (ACEI), both commonly used in CAPD patients, can influence lymphocyte subset counts (SLC). Previous studies indicate that rHuEPO (1–4), as well as ACEI (5), influence TLC and SLC in nondialyzed and hemodialyzed patients.

PATIENTS AND METHODS

The study was carried out in 55 patients being treated with CAPD and in 15 patients immediately prior to initiation of CAPD (group 0). The CAPD patients were divided into four groups, depending on dialysis duration. Group A consisted of patients treated for 6 to 12 months (n = 15); group B, for 13 to 24 months (n = 15); group C, for 25 to 36 months (n = 15); and group D, for more than 36 months (n = 10). In 12 patients treated with CAPD through 15.7 ± 8.1 months, the examinations were repeated at 29.3 ± 8.6 months of CAPD therapy.

Before starting dialysis, no CAPD patients (n = 55) had been receiving rHuEPO, but 15 patients had been receiving ACEI. During the course of CAPD, 34 persons received rHuEPO and 38 persons received ACEI. The percentage of patients continuously or tempo-

rarily receiving subcutaneous doses of rHuEPO was 40%, 60%, 73%, and 80% in groups A to D, respectively. The rHuEPO doses, calculated for the entire CAPD course and including periods without rHuEPO, were 2884 U, 3177 U, 6695 U, and 6279 U per CAPD month in groups A to D, respectively. Patients treated with rHuEPO were simultaneously taking an oral drug containing iron (210 mg Fe^{2+} daily) and folic acid (0.70 mg daily). Serum ferritin level was 231 ng/mL (median), range 180 – 3830 ng/mL. In 35 of 55 CAPD patients, enalapril was used as ACEI, 1 patient was receiving captopril, and 2 were receiving perindopril. In group A, 80% of patients were using ACEI (dose 243 mg); in group B, 73% (dose 275 mg); in group C, 80% (dose 211 mg); and in group D, 73% (dose 309 mg). Doses of ACEI are also expressed per CAPD month, including periods of CAPD treatment without ACEI administration. In the entire group of 55 CAPD patients, 7 patients were taking rHuEPO but not ACEI, 11 patients were taking ACEI but not rHuEPO, 27 patients were taking rHuEPO and ACEI, and 10 patients had never received rHuEPO or ACEI.

Percentages of SLC were determined by flow cytometry, using commercially available monoclonal antibodies: CD3, CD4, CD8, CD19, CD16+56 (Becton Dickinson, San Jose, California, USA). Granulocytes and monocytes were excluded from calculations with the help of monoclonal antibodies CD45 and CD14 (Becton Dickinson). Absolute counts of lymphocytes were calculated using white blood cell counts, estimated using routine procedures (stained smears and chamber method). In our laboratory, the normal range for TLC is $1.5 - 3.5 \times 10^9$/L; for CD3 cells (pan T cells), $1.1 - 1.7 \times 10^9$/L; for CD4 cells (helper T cells), $0.7 - 1.1 \times 10^9$/L; for CD8 cells (cytotoxic-suppressor T cells), $0.5 - 0.9 \times 10^9$/L; for CD19 (B cells), $0.2 - 0.4 \times 10^9$/L; and for CD16+56 cells (natural killer cells), $0.2 - 0.4 \times 10^9$/L. The normal CD4/CD8 ratio is 0.8 – 2.2.

Descriptive data are reported as mean ± 1 standard deviation of the mean. Results of TLC and SLC in all patient groups were compared to their respective normal ranges and to each other using the Kruskal–Wallis test. Comparative results were considered significant if the p value was below 0.05. Correlations between dialysis duration, SLC, rHuEPO, and ACEI doses were checked using the Spearman test.

RESULTS

The lowest values of TLC and SLC were observed immediately before initiation of CAPD. After 6 to 12 months of CAPD therapy, TLC, CD3, CD16+56, and CD4/CD8 ratio were within the normal range. In subsequent years of CAPD therapy, CD4, CD8, and CD19 cell counts were below the normal range, whereas mean TLC and CD3 were maintained within the normal range. The CD16+56 cell count exceeded the upper limit of normal in patients treated for more than 36 months. Significant differences were shown only between the TLC and SLC values obtained immediately before initiation of CAPD and those values obtained during CAPD therapy. There were no significant differences between TLC and SLC during the course of CAPD (Table 1). Repeated examinations performed in 12 patients after approximately 14 months of CAPD therapy also did not reveal significant differences in TLC or SLC.

In the entire group of CAPD patients, correlation was seen between dialysis duration and rHuEPO dose from the initiation of CAPD to the time of SLC estimations ($r = 0.049$, $p = 0.006$, $n = 55$), and between total rHuEPO and ACEI doses ($r = 0.279$, $p = 0.039$, $n = 55$). A significant correlation was also seen between dialysis duration and CD19 cell count ($r = -0.319$, $p = 0.018$, $n = 55$).

Table 2 presents absolute numbers of TLC and SLC in the four groups of CAPD patients relative to drug (rHuEPO, ACEI) administration. In patients taking ACEI but not rHuEPO ($n = 11$), correlation was shown between summarized ACEI doses and CD16+56 cell count ($r = -0.709$, $p = 0.014$). In patients that were receiving neither rHuEPO nor ACEI, there was a negative correlation between dialysis duration and TLC ($r = -0.709$, $p = 0.022$, $n = 10$), CD3 cell count ($r = -0.680$, $p = 0.030$, $n = 10$), and CD8 cell count ($r = -0.757$, $p = 0.011$, $n = 10$).

DISCUSSION

The significant positive correlation between dialysis duration and rHuEPO doses in our patients reflects the usual practice of increasing the dose of rHuEPO during the course of CAPD therapy. Despite this increase, a worsening of parameters of immunity and nutrition is observed with prolongation of dialysis treatment. Increased lymphocyte apoptosis leading to a decreased number of lymphocytes in the peripheral blood has been shown in patients on maintenance hemodialysis (6). Early detection of immunologic disturbances and features of malnutrition may be indicators to initiate clinical intervention, which would result in more-effective treatment with peritoneal dialysis. Repeat determinations of SLC seem to be helpful in the early diagnosis of such disturbances.

In our study, a significant negative correlation between CAPD duration and TLC or SLC was shown, especially in patients receiving neither rHuEPO nor ACEI. Administration of drugs can influence a natural decrease in TLC or SLC observed during the course of CAPD. Previous data indicate an increasing effect of rHuEPO on TLC (7), CD3 (2), CD4 (4), CD8 (3),

TABLE 1
Total Lymphocyte Count (TLC) and Lymphocyte Subset Counts in Peripheral Blood from Uremic Patients Immediately Before and During Continuous Ambulatory Peritoneal Dialysis (CAPD)

	Lymphocytes (10^9/L)				
		For CAPD duration (months)			
	Immediately before beginning CAPD (*n*=15)	6–12 (*n*=15)	13–24 (*n*=15)	25–36 (*n*=15)	37–52 (*n*=10)
TLC	1.02±0.47[a]	1.91±0.72[b]	1.51±0.41[b]	1.52±0.47[b]	1.82±0.76[b]
CD3	0.77±0.38[a]	1.37±0.57[b]	1.11±0.36[b]	1.12±0.35[b]	1.17±0.53[b]
CD4	0.31±0.16[a]	0.62±0.31[a,b]	0.52±0.19[a,b]	0.50±0.19[a,b]	0.46±0.24[a]
CD8	0.27±0.19[a]	0.37±0.20[a]	0.30±0.14[a]	0.34±0.15[a]	0.37±0.17[a]
CD19	0.06±0.04[a]	0.16±0.10[a,b]	0.09±0.04[a]	0.11±0.08[a]	0.09±0.06[a]
CD16+56	0.16±0.14[a]	0.35±0.15[b]	0.28±0.13[b]	0.24±0.15	0.42±0.36[b,c]
CD4/CD8 ratio	1.52±1.21	1.81±0.74	1.87±0.83	1.63±0.83	1.30±0.37

[a] Mean value below normal range.
[b] $p < 0.05$ compared to results before initiation of CAPD.
[c] Mean value above normal range.

TABLE 2
Total Lymphocyte Count (TLC) and Lymphocyte Subset Counts in Peripheral Blood from Continuous Ambulatory Peritoneal Dialysis Patients Grouped According to Drug [Recombinant Human Erythropoietin (rHuEPO), Angiotensin-Converting Enzyme Inhibitors (ACEI)] Administration

	Lymphocytes (10^9/L)			
	Drug administered			
	rHuEPO only (*n*=7)	ACEI only (*n*=11)	rHuEPO and ACEI (*n*=27)	No drugs (*n*=10)
TLC	1.57±0.36	1.67±0.69	1.58±0.64	1.87±0.71
CD3	1.14±0.30	1.24±0.60	1.07±0.42[a]	1.39±0.52
CD4	0.46±0.13[a]	0.61±0.32[a]	0.45±0.20[a]	0.67±0.26[a]
CD8	0.40±0.12[a]	0.31±0.18[a]	0.32±0.16[a]	0.37±0.16[a]
CD19	0.09±0.02[a]	0.12±0.09[a]	0.09±0.06[a]	0.17±0.11[a]
CD16+56	0.30±0.09	0.27±0.12	0.33±0.26	0.27±0.16

[a] Mean value below normal range.

and CD16 (1) cell counts, as well as CD4/CD8 ratio (1,4). Deterioration of nutrition, usually associated with more severe anemia, leads to an increase in rHuEPO doses. We suspect that a nearly stable (non-significantly decreased) CD4/CD8 ratio during the course of CAPD treatment reflects the effect of rHuEPO, which protects against the significant decrease in CD4/CD8 ratio that occurs with worsening nutritional status. A direct relationship between rHuEPO doses and/or TLC or SLC was, however, not shown.

In the patients examined, we observed an increase in the number of natural killer cells over the normal range within the length of time on CAPD. This finding is in accord with the study performed in CAPD patients by Palop and Martinez (8). Natural killer cells and their precursors are more resistant to immunosuppressive agents than are other immunocompetent cells, so suppressive uremic toxins affect the T lymphocyte number and function more effectively than they affect the number and function of natural killer cells (9). In patients on peritoneal dialysis, episodes of peritonitis and exit-site and tunnel infections may stimulate production of natural killer cells.

In our patients receiving ACEI but not rHuEPO, a significant negative correlation was shown between summarized ACEI doses and natural killer cell count. It was demonstrated in an earlier study that administration of ACEI, causing an increase in serum bradykinin concentration, might decrease T lymphocyte proliferation (5). ACEI can also abolish a positive effect of rHuEPO on bone marrow. Patients treated with ACEI may require higher rHuEPO doses during the course of peritoneal dialysis (10). On the other hand, positive correlation between rHuEPO and ACEI doses can indicate a necessity for increments in antihyper-

tensive drug doses, due to an increase in blood pressure related to rHuEPO administration or to difficulties in proper dehydration of patients while peritoneal membrane permeability increases during the course of CAPD.

CONCLUSION

rHuEPO and ACEI can influence total lymphocyte count and lymphocyte subset counts over the course of CAPD, disturbing their natural changes that occur with prolongation of CAPD treatment. The possibility of this influence should be taken into account when evaluating lymphocyte counts as indices of immune/nutritional status.

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Serum CrossLaps as Bone Resorption Marker in Peritoneal Dialysis

Chronic renal failure is often associated with skeletal disorders characterized by either high bone turnover, such as that produced by secondary hyperparathyroidism, or low turnover lesions, such as osteomalacia and adynamic bone disease (1). Accurate distinction between these two groups of disorders requires a bone biopsy examined with double tetracycline labeling.

In recent years, there has been a search for noninvasive methods to assess bone metabolism to distinguish between high and low turnover renal osteodystrophy in dialysis patients. One recent development has been the serum-based immunoassay for the bone resorption marker, C-terminal cross-linking telopeptide of type I collagen (CrossLaps; serum CTX) (2).

The aim of the present study was to compare serum CTX, a bone resorption marker, with validated biochemical markers of bone remodeling in peritoneal dialysis (PD) patients.

MATERIALS AND METHODS

Subjects: We studied 40 patients from a single center: 30 women (7 pre- and 23 postmenopausal) and 10 men. Patients were 51.9 ± 14.3 years of age and had been on PD for a mean of 29 months (range 3 – 77 months); 82% had previously been on hemodialysis for a mean of 58 months (range 1 – 316 months). The patients had not been hospitalized in the previous 3 months, 3 had been transplanted, and 1 had had parathyroidectomy. Dialysate calcium was 3.5 mEq/L

in 82.5% of the patients and 2.5 mEq/L in the rest; 89% of the patients were taking calcium-containing phosphate binders (mostly calcium carbonate) and 5% were taking aluminum hydroxide; 37% were taking low doses of vitamin D analogues. Patients were classified as having low bone turnover if their intact parathyroid hormone (iPTH) was less than 150 pg/mL or their bone alkaline phosphatase (BAP) was below 27 U/L. Patients having iPTH and BAP above these values were considered to have normal/high bone turnover.

Biochemical Determinations: Serum CTX was measured using two-site ELISA (Serum CrossLaps One Step ELISA; Osteometer BioTech A/S, Herleb, Denmark). Intact PTH was measured using an immunoradiometric assay (Nichols, San Juan Capistrano, California, USA); normal range 23 - 65 pg/mL. Bone alkaline phosphatase was measured by ELISA (Alkphase-B; Metra Biosystems, Mountain View, California, USA).

Statistics: All analyses were performed using CSS Statistica software (StatSoft, Tulsa, Oklahoma, USA). Data are presented here as mean ± SD. Comparisons between groups were analyzed using unpaired t-test. Correlations between different variables were assessed using linear regression analysis.

RESULTS

Patients on PD had serum CTX values ranging from 2166 to 90 840 pmol/L, mean 20 949 pmol/L. Females had mean serum CTX of 22 155 pmol/L (premenopausal 37 949 pmol/L; postmenopausal 17 348 pmol/L); males had mean values of 17 331 pmol/L. Patients older than 60 years of age (n = 10) had serum CTX values of 5183 ± 3092 pmol/L, significantly lower than those of younger patients (n = 30; 26 204 ± 22 854 pmol/L, $p < 0.01$).

Twenty-three patients (57.5%) were classified as having low bone turnover because they had either a low BAP or a low iPTH. These patients had serum CTX of 8778 ± 6764 pmol/L, significantly lower than patients classified as having normal/high bone turnover (37 416 ± 24 397 pmol/L, $p < 0.0001$). Only 9 patients (22.5%) had both low BAP and low iPTH. These patients had serum CTX of 5494 ± 3109 pmol/L. Serum CTX had a high correlation with iPTH (r = 0.87, $p < 0.0001$) and with BAP (r = 0.65, $p < 0.0001$).

DISCUSSION

In recent years, it has become possible to estimate the degree of bone resorption by measuring serum levels of tartrate-resistant acid phosphatase (3) or one of the multiple products of type I collagen degradation. These markers include nonreducible pyridinoline (PYD) and deoxypyridinoline (DPD) crosslinks (4), generally measured in hydrolyzed urine samples by HPLC or ELISA, and the related type I collagen telopeptides. Most of these collagen degradation products are urine markers that are unsuitable for dialyzed subjects.

Telopeptides are small amino acid sequences originating from the C terminal or N terminal nonhelical ends of collagen molecules. They are released into the circulation after degradation of mature collagen molecules of the bone matrix and can be measured in serum (5). Serum CTX has shown to be useful as a bone resorption marker for monitoring response in patients undergoing antiresorptive therapy for osteoporosis (6).

In the present study, we measured serum CTX in a stable population of patients on PD. Patients' mean serum CTX levels were 10 times those observed in a normal population (5). Couttenye *et al.* (7) recently demonstrated that a low BAP (≤ 27 U/L) and a low iPTH (≤ 150 pg/mL) had good sensitivity and specificity for adynamic bone disease, the most frequent form of low turnover renal osteodystrophy. Using these cutoff values, we found that patients having either a low BAP or a low PTH had serum CTX significantly lower than the patients we considered to have normal/high bone turnover; patients having both low BAP and low iPTH have even lower CTX values. Older age is generally considered a risk factor for low bone turnover and adynamic bone disease. In this study, older patients had also significantly lower serum CTX values than younger patients. Recently, Malyszko *et al.* found positive correlations of two other markers of bone resorption, serum ICTP and urine DPD, with serum CTX in PD patients (8).

Our study suggests that measurement of serum CTX is at least as good as BAP or iPTH as a diagnostic tool to assess bone turnover in patients undergoing PD. Our results have to be considered only preliminary as serum CTX values have not been compared with direct measurements, by activation frequency, of bone turnover in bone biopsies.

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Do Patients Referred Late for Peritoneal Dialysis Do Badly?

In the second edition of their "Standards Document" (1), the Renal Association (UK) recommends referral of patients with chronic renal failure to specialist nephrology clinics. The advantages of early referral include the ability to start patients on dialysis before they become symptomatic and to prepare them medically and psychologically for dialysis — aspects of care proposed in the recent report from The UK Kidney Alliance to form part of a National Service Standard (2). It has been shown that hemodialysis (HD) patients that are referred late (thus requiring temporary intravascular catheters for the commencement of dialysis) have more complications than matched patients that attend specialist clinics (3,4). A survey of referral patterns to nephrologists defined "late" referrals as those patients that required dialysis within 1 month. This study documented wide variation in the proportion of "late" referrals, ranging from 10% to 51% across Europe (5). Contrary to the commonly held perception that "late" referral is a strong determinant of dialysis modality, with only a minority of patients choosing peritoneal dialysis (PD), Winkelmayer *et al.* (6) showed that late referral did not influence the initial choice of modality. Late referral means that the patients either start PD after a few weeks of HD, or they avoid HD altogether. In both scenarios, patients do not attend the formal predialysis education that occurs in multidisciplinary nephrology clinics.

We examined whether patients that start PD but are referred late have more complications (peritonitis, PD failure, or mortality) than do patients that attended our nephrology clinics.

METHODS

A retrospective analysis of all patients starting dialysis at St Bartholomew's and The Royal London Hospital between 1 June 1998 and 1 August 1999 was performed. Two hundred and eleven patients started dialysis over this period. Of the 107 patients that started PD for the first time, 9 patients were established on HD for over 30 days and were excluded from further analysis. A further 71 patients ("planned") attended a nephrology clinic at least 30 days prior to dialysis, and 27 patients ("late referral") started on PD within 30 days of referral. All patients were given a choice of dialysis modality, although there were severe resource pressures on HD capacity during the study period. Those patients that were referred late but needed urgent dialysis were hemodialyzed and the patients' final decisions regarding modality were made after consultation with our dialysis counselors, who are renal specialist nurses. "Planned" patients underwent predialysis education with the nurse and a dietician — the majority within the setting of a formal "low clearance" clinic. "Late referral" patients underwent similar programs, although the urgency of dialysis would have placed important time constraints on the counselors.

Demographic details and predialysis biochemical parameters were recorded. Using patient records, we obtained details of deaths, failure of PD, and episodes of peritonitis over the 12 months following initiation of PD.

Statistical tests used to compare the two groups were chi-square, Fisher's exact test, and Student's t-tests; *p* values less than 0.05 were used to denote statistical significance.

RESULTS

The patient characteristics of the two groups are shown in Table 1. There was no significant difference in mean age, sex ratio, or incidence of diabetes mellitus between the "planned" and "late referral" groups. In the "planned" group, 4 elected to start on automated peritoneal dialysis (APD) using a HomeChoice machine (Baxter, Northampton, UK). One of the 27 "late referral" patients was started on APD. In the "planned" group of patients, the mean (±SEM) duration of attendance in nephrology clinics was 482 ± 70 days.

Predialysis biochemical parameters of the "planned" and "late referral" groups are shown in Table 1. The "planned" group had significantly lower serum creatinine and urea concentrations than the "late referral" group. Conversely, serum bicarbonate and hemoglobin concentrations were significantly higher in the "planned" group.

Peritonitis and outcome data for these patients are shown in Tables 2 and 3. During a 1-year follow-up period, the "planned" group had a peritonitis rate of 1 in 27.5 months. In the "late referral" group of patients, the peritonitis rate was 1 in 19.8 months. Odds ratio analysis showed that patients that were referred late had a nonsignificantly increased risk of peritonitis within the first year of dialysis (relative risk ratio 1.18, 95% confidence interval 0.826 – 1.694). There was also no significant difference in the number of patients with more than 1 episode of peritonitis (*p* = not significant; Fisher's exact test).

TABLE 2
Number of Patients with Episodes of Peritonitis at 1-Year Follow-up

	Episodes				
	0	1	2	3	4
"Planned" (*n*=71)	46	22	1	1	1
"Late referral" (*n*=27)	15	8	3	1	0

TABLE 3
Outcome of Patients After 1-Year Follow-up

	Modality at 1-year				
	PD	HD	Tx	Died	Other
"Planned" (*n*=71)	63	2	3	2	1
"Late referral" (*n*=27)	20	2	3	2	0

PD = peritoneal dialysis; HD = hemodialysis; Tx = transplanted.

Of the 71 "planned" patients, 63 remained on PD at the end of the study period, 2 had been transferred to HD, 3 had been transplanted, 2 had died, and 1 had transferred to another dialysis unit for geographic reasons. Of the 27 "late referral" patients, 20 remained on PD, 2 had been transferred to HD, 3 had been transplanted, and 2 had died. By chi-square analysis, there was no significant difference in outcome between the two groups.

DISCUSSION

Patients that are referred late to specialist nephrology clinics have greater morbidity and mortality during the first year of HD (7), but there are no data on the effect of referral patterns on the out-

TABLE 1
Demographic and Laboratory Details of Patients Starting Peritoneal Dialysis (Mean ±SEM). *p* Values (unless stated) were calculated using Student's t-test.

	"Planned" (*n*=71)	"Late referral" (*n*=27)	*p* Value
Age (years)	51.1±1.7	51.5±3.4	NS
Gender (M:F)	40:31	18:9	NS by chi-square
Patients with diabetes mellitus (*n*)	17	8	NS by chi-square
Serum creatinine (μmol/L)	854±32	985±69	0.05
Serum urea (mmol/L)	35.0±1.1	43.3±3.4	<0.005
Serum bicarbonate (mmol/L)	22.0±0.5	19.1±0.9	<0.0005
Serum albumin (mmol/L)	36.6±0.7	36.0±0.9	NS
Hemoglobin (mg/dL)	10.3±0.3	7.9±0.3	<0.0001

NS = not significant.

come of patients starting PD. The "planned" and "late referral" groups in our study were similar with respect to age, sex, and incidence of diabetes. At the time of starting dialysis, those patients that were referred "late" (required dialysis within 30 days of referral) had significantly higher serum creatinine and urea concentrations and were more acidotic and anemic than those patients that attended specialist nephrology clinics for a mean of 482 ± 70 days. Other factors that would be expected to differ in these two patient groups might be early subcutaneous leaks and drainage problems. We did not confirm this in our study as the confounding factors of earlier catheter use and smaller volume of initial exchanges may have made interpretation difficult.

Albeit a study of limited size, our data suggest that patients that were referred late but elected to have PD did not have any greater mortality or morbidity (measured by peritonitis rates and technical failure rates). A study of this size (approximately 100 patients) is powered ($p < 0.05$) to detect an increase of 40% in the peritonitis rate. Our results show that 44% of patients referred late had at least 1 episode of peritonitis after 1 year, compared with 35% of "planned" patients. This difference (9%) was not statistically significant. In order to be powered to detect such a difference (at 99% confidence interval), 2870 patients would have been required. The results of our study contrast with the results of a smaller study ($n = 40$) that demonstrated statistically significant poorer outcomes in "late referred" patients compared with "planned" patients on HD (8). Of course, it would have been preferable if our outcome data were controlled for comorbidity (*e.g.*, Charlson Comorbidity Index). We only attempted to confirm that the incidence of diabetes mellitus was the same in the two groups because collecting details of comorbidity retrospectively would have been fraught with inaccuracies. The patients that were referred late but that elected to have PD may be a select group that was well motivated. This might explain why their outcomes were comparable to patients that had been attending the specialist nephrology clinics.

Although early referral should be made where possible, there are many reasons why patients continue to be referred "late" (9). It is reassuring that our preliminary data suggest that treatment of these patients by PD is both effective and safe. Moreover, a recent study concluded that, overall, within the first 2 years of therapy, PD appeared to be associated with superior outcomes compared with HD (10). Patients transferred from PD to HD in a "timely manner" have also been shown to have the best survival (11). A prospective study to determine whether patients that are referred late and start "acute PD" have superior outcomes to patients starting "acute HD" is in progress.

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