Automated vs continuous ambulatory peritoneal dialysis: a systematic review of randomized controlled trials

Kannaiyan S. Rabindranath, James Adams, Tariq Z. Ali, Conal Daly, Luke Vale and Alison M. MacLeod

1Renal Unit, Churchill Hospital, Oxford, 2Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, 3Renal Unit, Western Infirmary, Glasgow and 4Health Economics Research Unit, University of Aberdeen, Aberdeen, UK

Abstract
Background. A systematic review of randomized controlled trials (RCTs) comparing continuous ambulatory peritoneal dialysis (CAPD) with all forms of automated peritoneal dialysis (APD) was performed to assess their comparative clinical effectiveness.

Methods. The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, were searched for relevant RCTs. Analysis was by a random effects model and results expressed as relative risk (RR) and weighted mean difference (WMD) with 95% confidence intervals (CI).

Results. Three trials (139 patients) were identified. APD when compared to CAPD was found to have significantly lower peritonitis rates (two trials, 107 patients, rate ratio 0.54, 95% CI 0.35–0.83) and hospitalization rates (one trial, 82 patients, rate ratio 0.60, 95% CI 0.39–0.93) but not exit-site infection rates (two trials, 107 patients, rate ratio 1.00, 95% CI 0.56–1.76). However no differences were detected between APD and CAPD in respect to risk of mortality (RR 1.49, 95% CI 0.51–4.37), peritonitis (RR 0.75, 95% CI 0.50–1.11), switching from the original peritoneal dialysis (PD) modality to a different dialysis modality including an alternative form of PD (RR 0.50, 95% CI 0.25–1.02), PD catheter removal (RR 0.64, 95% CI 0.27–1.48) and hospital admissions (RR 0.96, 95% CI 0.43–2.17). Patients on APD were found to have significantly more time for work, family and social activities.

Conclusions. APD appears to be more beneficial than CAPD, in terms of reducing peritonitis rates and with respect to certain social issues that impact on patients’ quality of life. Further, adequately powered trials are required to confirm the benefits for APD found in this review and detect differences with respect to other clinically important outcomes that may have been missed by the trials included in this review due to their small size and short follow-up periods.

Keywords: ambulatory peritoneal dialysis (APD); continuous ambulatory peritoneal dialysis; (CAPD), systematic review; meta-analysis; clinical outcomes; peritonitis

Introduction
Peritoneal dialysis (PD) has been used as an alternative to haemodialysis (HD) for the treatment of end-stage renal disease (ESRD) for almost three decades [1]. Continuous ambulatory peritoneal dialysis (CAPD) involves performing the PD exchanges manually, whereas automated peritoneal dialysis (APD) is a broad term that is used to refer to all forms of PD employing a mechanical device to assist the delivery and drainage of dialysate. The various forms of APD include continuous cyclical PD (CCPD), intermittent PD (IPD), nightly intermittent PD (NIPD) and tidal PD (TPD). In CAPD, the patient or carer must perform at least 4–5 exchanges everyday. Many problems inherent to CAPD such as lack of sustained patient motivation over long periods of time, technique failure and recurrent peritonitis, led to a resurgence of interest in APD and the introduction of CCPD in 1981 by Diaz-Buxo and colleagues [2]. APD has been reported to have several advantages over CAPD including lower incidence of peritonitis, [3,4] better small solute clearances [5] and reduced incidences of hernias [6]. APD, especially in the form of NIPD, has also been suggested to offer a number of psychosocial and physical benefits over CAPD mainly on account of fewer connections and being free of fluid in the abdomen during daytime. Such benefits relate to better dialysis acceptability for workers, school pupils or carers of elderly or debilitated patients, reduced back pain and body image difficulties and reduced

This work was performed at Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, UK.

Correspondence to: Kannaiyan S. Rabindranath, MBBS, MRCP, Renal Unit, Churchill Hospital, Oxford OX3 7LJ, UK.

Email: ksrabi@yahoo.co.uk

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intra-abdominal pressures [7,8]. APD is also considered to be more suitable form of PD in patients who have a rapid rate of solute transfer across their peritoneal membrane (high transporters) because of the ability to perform rapid frequent exchanges with shorter dwell times [9]. APD has in fact been proposed as an alternative to CAPD in all patients for whom PD is considered suitable [10]. The Renal Association (UK) and the European Best Practice Guidelines for peritoneal dialysis recommend APD for PD patients who have high peritoneal transporter status, in those with need to avoid high intra-peritoneal pressures and in patients who need it for psychosocial reasons [9,11]. The main adverse effect reported with APD has been a more rapid decline in residual renal function, when compared to CAPD [12, 13].

The proportion of PD patients on APD has been steadily increasing over the past decade. In the US, the percentage of PD patients on APD has steadily risen from 9% in 1993 to 28% in 1997 and to 54% in 2000 [14, 15]. The direct costs of APD are over 20% greater than CAPD [16]. Given this increasing trend towards greater use of APD, it is important to know if the proposed psychosocial and clinical benefits of APD are realized when compared to CAPD and whether it is associated with an increased risk of accelerated residual renal function decline.

Methods

Inclusion criteria

We included randomized controlled trials (RCTs) comparing CAPD with any form of APD.

Search strategy

Electronic searches were performed in MEDLINE (1966 to May 2006), EMBASE (1980 to May 2006), the Cochrane Central Register of Controlled Trials (CENTRAL) (up to May 2006) and the Cumulative Index to Nursing & Allied Health Literature (CINAHL) (up to May 2006) by using optimally sensitive search strategies for identification of RCTs developed by the Cochrane Collaboration [17]. The following medical subject heading terms and text words were used: kidney failure, uraemia and peritoneal dialysis. Additionally, relevant textwords relating to all investigated interventions were used. Based on standard systematic review methods, results of these searches were screened initially in their title and abstract form by two of the authors (K.S.R., T.Z.A.) according to inclusion criteria. Studies that clearly did not meet the inclusion criteria (i.e. animal studies, non-RCTs, RCTs of interventions that were not declared ‘a priori’ in the inclusion criteria for this review) were not considered further. The full-text was analysed when there was doubt.

Data extraction and quality assessment

Two independent reviewers (K.S.R., T.Z.A) assessed each trial for eligibility criteria, and discrepancies were solved in consultation with a third investigator (A.M.M). From all included RCTs, the data extracted were by two authors (K.S.R., J.A.) independently on the following outcomes when they were reported: infections (PD-related peritonitis, exit-site and tunnel infections), PD-catheter changes, mechanical complications (abdominal hernias, hydrothoraces and exit-site leaks), incidence of technique failure, dialysis adequacy measures (Kt/V and weekly creatinine clearance), hospitalization (number of patients hospitalized, number of hospitalization episodes and number of days of hospitalization), quality of life (whatever measure used), mortality, endogenous creatinine clearance and blood pressure (systolic, diastolic and mean arterial).

Method quality of the included RCTs was assessed by using standard criteria looking for the following: (i) allocation concealment (whether the randomisation method adequately prevented the investigator from influencing the allocation of patients to the experimental interventions); (ii) blinding of participants, investigators and outcome assessors; (iii) use of intention-to-treat analysis; and (iv) completeness of follow-up. When data were missing or incomplete, investigators of the trials were contacted by written correspondence for clarification.

Statistical analysis

Treatment effects were summarized with the relative risk (RR) measure and its 95% confidence intervals (CI) for dichotomous outcomes and the weighted mean difference (WMD) and its 95% CI for continuous outcomes. The estimates from individual RCTs were pooled using the DerSimonian and Laird random-effects model when appropriate. The Mantel–Haenszel fixed-effect model was also computed to evaluate robustness and susceptibility to outliers. Where data on the number of episodes were available, the rate ratio was calculated as the ratio of the rate of the outcome (e.g. the peritonitis rate) in the experimental treatment group (given by number of episodes of the outcome over unit time on PD) over the rate in the control group. The generic inverse variance method was used to calculate rate ratios and their 95% CI. The rate ratio shows the reduction in the incidence rate in the experimental intervention group compared to that in the control intervention group. For example, a rate ratio of 0.6 indicates a 40% reduction in events in the experimental intervention group compared to those on the control intervention. Heterogeneity of treatment effects between studies was formally tested using the Q (heterogeneity $\chi^2$) and the I$^2$-statistics. Subgroup analysis was planned to explore how possible sources of heterogeneity (diabetic status, peritoneal solute transporter status) might have influenced treatment effect. It was also planned that if sufficient RCTs were identified, an attempt would be made to assess publication bias using a funnel plot. All analyses were undertaken using RevMan 4.2.8 (© 2005, The Cochrane Collaboration, UK).

Results

The combined search identified 311 potentially relevant studies out of which 287 studies were initially excluded. The full-text versions of 24 studies were retrieved, 16 of which were subsequently excluded (Figure 1). The major reasons for exclusion were...
Flow chart indicating the number of citations retrieved by individual searches and the final number of included trials; reasons for exclusions are provided.

Fig. 1. Flow chart indicating the number of citations retrieved by individual searches and the final number of included trials; reasons for exclusions are provided.

Table 1. Characteristics of the populations in the randomized controlled trials included in this review

<table>
<thead>
<tr>
<th>Study ID</th>
<th>No. of patients</th>
<th>Population characteristics</th>
<th>Cause of renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DM</td>
</tr>
<tr>
<td>Bro et al. 1999</td>
<td>34</td>
<td>APD: Mean age: 54.20 years; 8 males, 5 females</td>
<td>●</td>
</tr>
<tr>
<td>De Fijter et al. 1994</td>
<td>97</td>
<td>APD: Mean age: 50.20 years; 8 males, 4 females</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAPD: Median age: 55.50 years; 27 males, 23 females</td>
<td>●</td>
</tr>
<tr>
<td>Iles-Smith et al. 1999</td>
<td>8</td>
<td>APD: Mean age: 42.00 years; 2 males, 1 females</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAPD: Mean age: 53.00 years; 5 males, 0 females</td>
<td></td>
</tr>
</tbody>
</table>

Filled circles indicates that the study population included with those conditions, i.e. diabetes, hypertension, etc. DM, diabetes mellitus; HTN, hypertension; GN, glomerulonephritis; NA, data not available.

(i) studies were not randomized (ii) the interventions assessed or the outcomes reported were not relevant to this review and (iii) review articles. Finally, three trials published in eight reports met the inclusion criteria [16,18,19]. The characteristics of the populations in the included trials are reported in the Table 1.

Authors of all included trials were contacted for clarification regarding trial methodology and additional unpublished data. Two replied to our queries. All three studies had a parallel design [16,18,19].

**Trial characteristics**

Table 2 lists the study design, quality assessment and characteristics of the interventions administered in the RCTs included in this review. Not all outcomes were analysed or reported by each individual trial.

The mean age of the study populations ranged from 42.00 to 54.20 years. None of the other trials mentioned whether patients received any other interventions apart from the dialysis modality such as erythropoietin, phosphate binders and anti-hypertensives.

**Trial quality**

All three studies had an adequate method of allocation concealment. The method of allocation concealment in two studies was obtained by contacting the authors [18,19]. In two studies [18,19], allocation concealment was by using sealed envelopes and in another [16]...
it was centralized randomization using permuted blocks stratified according to clinical centre, age and diabetic status. Due to the nature of the investigation we did not expect blinding of participants and investigators. None of the studies reported blinding of outcome assessors. None of the trials were analysed on an intention-to-treat basis.

Dropouts were defined as number of patients leaving the study for reasons other than death. A total of 67 out of 139 patients (48.20%) dropped out. Reasons for discontinuation of the study include the following: A break up for the different reasons are as follows: transplants—31, recovery of renal function—3, technique failure (peritonitis, poor ultrafiltration, general medical conditions and psychosocial reasons) —33.

**Trial results**

Only end-of-study results and patient numbers were used for the analysis.

Infectious complications (Figures 2 and 3). Three categories of infectious complications were considered and the data available for each varied. However, there was no evidence of heterogeneity between studies for any of these three complications. Patients on APD when compared to those on CAPD were found to have significantly lower rates of peritonitis (two studies, 107 patients, rate ratio 0.54, 95% CI 0.35–0.83), but not exit-site infection rates (two studies, 107 patients, rate ratio 1.00, 95% CI 0.56–1.76). There was no difference between APD and CAPD in terms of risk of patients developing peritonitis (three trials, 115 patients, RR 0.75, 95% CI 0.50–1.11), exit-site infections (two trials, 107 patients, RR 1.09, 95% CI 0.56–2.13) and tunnel infections (two trials, 107 patients, RR 0.99, 95% CI 0.15–6.49).

Change of dialysis modality (Figure 2). There was no difference in the risk of patients for switching from their original PD modality to a different dialysis modality including an alternative form of PD (three trials, 115 patients, RR 0.50, 95% CI 0.25–1.02). Likewise, patients on APD did not have a significantly lower risk of switching to HD alone (two trials, 107 patients, RR 0.45, 95% CI 0.16–1.28). There was no evidence of heterogeneity between the studies.

Hospital admissions (Figure 2). APD did not reduce the risk of hospital admissions compared with CAPD (two trials, 107 patients, RR 0.96, 95% CI 0.43–2.17). Heterogeneity was not significant across the two trials. Patients on APD had significantly lower hospitalization rates than those on CAPD (one study, 82 patients, rate ratio 0.60, 95% 0.39–0.93).

Quality of life. Only one study [18] reported data in a meta-analysable format. This study assessed quality of life using the Karnofsky score and there was no difference found between patients in either group (one trial, 24 patients, WMD 6.00, 95% CI 0.00–12.00). One study [19] showed that whilst patients on APD showed no change (group mean score 86.7) in Karnofsky scores between the start and end of study, those on CAPD experience a small decline (from 82.5 to 80). Another study [16] used the validated tool Short Form-36 (SF-36) to assess quality of life. Whilst there were no differences in the scores between patient groups in either PD-modality, patients on APD were found to have significantly more time for work, family and social activities ($P < 0.0005$).

The data on all other outcomes (mechanical complications, PD-catheter removal, dialysis adequacy, residual renal function, mortality, blood pressure) are given in Table 3.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Design</th>
<th>Duration of follow-up</th>
<th>Interventions assessed</th>
<th>Study quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bro et al. 1999 [16]</td>
<td>Parallel</td>
<td>6 months</td>
<td>APD to maintain normalized Kt/V $\geq 1.70$/week and total creatinine clearance $&gt;50$/week initially by NIPD alone and if this was not possible a last bag in the morning or a last bag in the morning plus an additional one in the afternoon was added</td>
<td>Regime not mentioned</td>
</tr>
<tr>
<td>De Fijter 1994 [18]</td>
<td>Parallel</td>
<td>CAPD—688 patient-months APD—723 patient-months</td>
<td>CAPD to achieve Kt/V of 2.1</td>
<td>Adequate</td>
</tr>
<tr>
<td>Iles-Smith 1999 [19]</td>
<td>Parallel</td>
<td>4 weeks</td>
<td>APD to achieve Kt/V of 1.9 or creatinine clearance of 60/l/week</td>
<td>Adequate</td>
</tr>
</tbody>
</table>
Discussion

Our review found that APD was associated with significantly lower peritonitis and hospitalization rates, when compared to CAPD. Data from our meta-analysis suggests that APD is associated with almost 40% lower peritonitis rates. This may be due to the fewer connections involved in performing APD. Significant differences with respect to other important clinical benefits such as risk of mortality, switching from their original PD modality to a different dialysis modality including an alternative form of PD, hernias, PD fluid leaks, PD catheter and hospital admissions were not made out by the studies between both APD and CAPD. Dialysis adequacy measures were also not different between both PD modalities. Whilst most of the quality of life measures were not different between patients on APD and CAPD, one study found that patients on APD had significantly more time for work, family and social activities [16].

The evidence with respect to the effect of APD on peritonitis when compared to CAPD is controversial with some studies favouring APD, [3,4,20] some CAPD, [21,22] and a few others finding peritonitis rates to be similar between both modalities [23–25]. These studies were all observational studies and hence prone to biases and their results may therefore not be entirely reliable. It is interesting to note that the results from our systematic review showed a significant reduction in peritonitis rates with APD, but no significant reduction in relative risk for patients on APD developing peritonitis. This may be because, in practice, not infrequently the same patients have more than one episode of PD-related infections. Therefore, it is
possible that the assessment of the relative effectiveness of the different PD modalities in terms of relative risk of patients acquiring PD-related infections may underestimate and consequently miss significant differences between the various PD modalities on these outcomes.

Analysis of a large cohort of patients (>30 000) starting PD over 3 years showed that in the first year of dialysis patients on APD had a significantly better patient and dialysis technique survival when compared to those on CAPD [26]. Although patients on APD were found to be younger than CAPD patients, the differences in patient and technique survival were significant even after adjustment for age and diabetes status. In contrast to this study, our evidence derived from randomized controlled studies did not show any advantage with APD with regard to patient or technique survival between APD and CAPD.

The CANUSA study and other studies have shown an increased mortality in CAPD patients with peritoneal membrane high or rapid solute transport characteristics [14,27]. Although APD may offer better small solute clearances in such patients compared to CAPD, there is no evidence so far that this translates to improved survival rates [28]. One study in our review included only patients with high or high-average peritoneal transport characteristics [16]. This study allowed us to explore the hypothesis that patients with such peritoneal transport characteristics might do better on APD than on CAPD. This study did not show any advantage with APD with regard to patient or technique survival in this specific PD population group but the study’s small patient population and short follow-up period may have precluded it from detecting any such advantage.

Preservation of residual renal function is of great importance as it has been shown to be a predictor of patient survival on PD [29]. Some studies have shown that APD is associated with a more rapid loss of residual renal function when compared to those on
CAPD [12,13]. However, subsequent studies have given contradictory results [30,31]. Results from our review did not show any difference in end-of-study period endogenous creatinine clearance, i.e. residual renal function, between either PD modality.

The strength of our analysis is that this article is a comprehensive up to date systematic review of randomized trials comparing APD and CAPD. We had rigid inclusion criteria including RCTs alone and have used a very comprehensive search strategy of all major medical electronic databases and other sources. The data from randomized trials have greater validity than observational studies as the process of randomization removes potential biases by ensuring that the patient groups are equal in terms of both known and unknown characteristics, and are therefore superior to data from observational studies.

Whilst the use of APD has been expanding rapidly, it is surprising to note that this systematic review identified only three RCTs with just 139 patients comparing it with CAPD, and none since 1999. The trials also showed considerable variability in their design conduct, and intervention protocols. The CIs for important outcomes such as dialysis modality change and peritonitis are wide enough to suggest that there may indeed be clinically important differences between APD and CAPD. The small sample sizes of the included trials would have, however, greatly reduced the power of these trials to detect such differences, i.e. increased the likelihood of type 2 statistical errors. Two of the three studies were less than a year in duration. Therefore, these trials are not appropriate for the assessment of long-term clinical outcomes. Almost half the study population (67 out of 139 patients) dropped out from the included studies and this high dropout rate might affect the validity of the study results. The results of this review should, therefore, be interpreted with caution owing to the inherent limitations of the included trials. It therefore does appear that the data from currently available RCTs is not sufficient enough for us to reach definitive conclusions about the relative clinical effectiveness of CAPD and APD with respect to important clinical outcomes.

There have been two economic evaluations comparing APD and CAPD. One evaluation showed that the cost for APD compared to CAPD per patient per year to prevent one episode of peritonitis was UK£11000 (1997 prices) [32]. The other economic evaluation which was done as part of the trial by the Bro et al. study showed that APD was 20% more expensive than CAPD [16]. Given the limitations of the trials identified in this review and the advances that have occurred in PD technology over the past 10 years, there is a great need for a large, well-designed, good quality RCT comparing APD with CAPD, looking at clinically important outcomes accompanied by an economic evaluation to reliably inform both patients and nephrologists about the relative clinical effectiveness of these PD modalities and the cost implications to health care providers. Such a trial could also be used to explore patient satisfaction and treatment preferences for these PD modalities. Future studies should take the high dropout rate noted in the previous trials and recruit a sufficiently large enough study population to offset the patients who are likely to be lost during the trial period.

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Conflict of interest statement. None declared.

(See related article by P. G. Blake et al. Randomized controlled trials in PD. Nephrol Dial Transplant 2007; 22: 2746–2749.)

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