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Review

Automated Peritoneal Dialysis: An alternative to Continuous Ambulatory or a First Choice Treatment?

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Abstract

The use of the various forms of Automated Peritoneal Dialysis (APD) has considerably increased in the past few years. This increase is driven by improved cycler design, apparent lifestyle advantages, and the increased ability to achieve adequacy and ultrafiltration targets. It is therefore reasonable to raise the question whether APD is superior to Continuous Ambulatory Peritoneal Dialysis (CAPD). APD is considered the most suitable Peritoneal Dialysis (PD) modality for high transporters as well as for assisted PD. It has also been associated with improved compliance, lower intraperitoneal pressure and possibly lower incidence of peritonitis. On the other hand, there are concerns regarding increased cost, a more rapid decline in residual renal function, inadequate sodium removal and disturbed sleep. Besides its beneficial results in high transporters, other medical advantages of APD still remain unclear. Individual patient's choice remains the most important indication for applying APD, which should be made available to all patients starting PD.

Key words: automated peritoneal dialysis (APD), continuous ambulatory peritoneal dialysis (CAPD), high transporters, patient selection

Introduction

The utilization of the various modalities of Automated Peritoneal Dialysis (APD) has increased considerably during the past few years. This upward trend could be mainly attributed to the improved cycler design as well as better adjustment of APD to patient's lifestyle. According to the ERA/EDTA Registry Annual Report for the year 2010, a significant increase in the utilization of APD has been noted in Europe. In Greece, 40% of patients who initiated peritoneal dialysis (PD) in 2010 were switched to APD (annual incidence). Fifty-eight percent (58%) of all PD patients utilized APD. This proportion varied between 40 to 50% in France, UK, Italy and the Netherlands. Moreover, in countries such as Belgium, Finland and Denmark, more than 60% of PD patients used APD [1]. In USA, the preference of APD as the modality of choice for patients being treated with PD was evident from the late 90s'. This fact together with the decline in the overall PD utilization, suggests that the development of APD was rather accomplished at the expense of CAPD. Thus according to the USRDS, the proportion of patients on APD in the USA increased from 47% in 2000 to 66% in 2009, while the overall proportion of patients undergoing PD (APD and CAPD) decreased from 8.9% to 6.9% during the same time period [2]. Accordingly, the percentages of APD in Canada were 43% in 2001 and 62% in 2010 [3]. In 2010, 61% and 43% of patients on PD underwent APD in Australia and New Zealand, respectively [4]. A recent epidemiological study [5] showed that the proportion of patients on APD is significantly smaller in the developing countries compared to the developed ones (15.8% in developing countries versus 42.4% in developed countries, of all patients on PD). It appears that the increase in APD utilization in the developed world is attributed mainly to patient's personal choice [6]. The predominance of APD over CAPD could not be supported by robust clinical evidence, but by the improved cycler design as well as the improvement of patient's quality of life [7].

Patient and technique survival

Whether APD is superior to CAPD regarding patient and technique survival remains to be elucidated. This question is hard to answer considering that the accomplishment of randomized controlled clinical trials is apparently difficult and moreover it is impossible to conduct blinded randomized controlled clinical trials. The results of the already available trials are controversial. The study of Guo and Mujais from the USA, which was based on the Baxter Healthcare Corporation On-Call TM system, including approximately 30.000 patients,

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showed improved patient and technique survival during the first year in patients on APD [8]. In a more recent trial, including approximately 40.000 patients, Mujais and Storey reported that APD has a dominant effect on technique success, with a relative risk of 0.845 compared to CAPD [9]. According to Australia and New Zealand Registry Report (ANZDATA), the ***application*** of ***APD*** had ***similar*** technique and ***patient survival*** with ***CAPD*** in ***4128 patients [4]***. A meta-analysis of 3 randomized controlled trials which compared CAPD to APD, including a total of 139 patients, did not show any benefit of either technique over the other regarding patient mortality or technique survival [10]. In particular, APD seems to be superior to CAPD regarding patient and technique survival in patients less than 65 years old [11]. A prospective trial, with 5-year follow-up (NECOSAD) showed similar results with respect to patient and technique survival [12]. The superiority of APD, with regards to technique survival, was shown by a trial based on a database of 620 patients from the USA [13], while a similar superiority of APD reported in a UK trial was lost after adjusting for comorbidities [14]. A recent trial from Thailand, in which 121 patients were retrospectively evaluated, showed that APD was associated with a lower risk of technique failure. Specifically, although there was no difference shown in the mortality risk, technique survival during the first 2 years was better in patients on APD compared to those on CAPD [15]. In conclusion, both methods do not seem to differ substantially regarding technique and patient survival, except a possible comparable advantage of APD in the subpopulation of high transporters.

APD and high transporters

The European Best Practice Guidelines-EBPG, acknowledge three main indications for APD application: patient's preference, the necessity to avoid increased intraperitoneal pressure and inability to achieve the targets of ultrafiltration and substance clearance, especially in high transporters [16]. Towards the same direction, the International Society of Peritoneal Dialysis ad hoc Committee on Ultrafiltration Management in Peritoneal Dialysis recommends the application of APD in cases of ultrafiltration loss in high transporters [17].

The status of high or more precisely rapid transport of substances across the peritoneal membrane is most probably the ideal circumstance when APD is indicated. The association between high peritoneal permeability with poor patient and technique survival in PD is already recognized [18-20]. Still, several clinical trials have shown that high transporters might benefit from the utilization of APD. The EAPOS trial showed that the baseline peritoneal membrane transport status does not correlate with the ultrafiltration rate achieved during the first year and it does not affect technique survival [21]. In a publication ensuing from the Oceania Registry (ANZDATA), an association between high peritoneal transport and worse outcomes was shown only in patients on CAPD and not in those on APD [20]. A more recent trial from Toronto has shown that a high peritoneal transport status does not constitute a risk predicttive factor of worse patient survival or technique failure in patients on APD, with or without icodextrin use [22]. Another trial including 4128 patients managed to show that APD is associated with a significant survival advantage in high transporters compared with CAPD. However, APD treatment was associated with inferior survival in low transporters. There was no difference observed between APD and CAPD in the same trial regarding technique survival [23]. Thus, the initial concern regarding clinical outcomes of high transporters undergoing PD seems to be how to overcome APD utilization in this subgroup of patients, regardless of the icodextrin use.

Peritonitis-exit site infections

Over a 24-hour period, APD involves one connection and one disconnection. On the other hand, CAPD involves on average four connections and four disconnections. It is obvious that the smaller number of manipulations required from patients on APD could probably result in a substantial reduction in the incidence of peritonitis [24]. Moreover, it has been demonstrated that white blood cell function is improved with prolonged dwell times of fluid in PD [25], such as the daily dwell in continuous cycling PD (CCPD). The peritoneal mesothelial cells show improved function after several hours of peritoneal membrane rest [26], as occurs during daytime with nocturnal intermittent PD (NIPD). Nevertheless, the delay in the diagnosis of peritonitis in APD raises several concerns. The evidence with respect to the effect of APD on peritonitis when compared to CAPD is controversial. A number of retrospective studies favor APD [27], some other favor CAPD [28,29], while other publications have shown that both methods are equivalent regarding the overall rate of peritonitis [30]. A large prospective non-randomized trial including 328 patients demonstrated similar rates of peritonitis and exit site infections for both modalities [31]. Nevertheless, a smaller trial (n=20) showed lower rates of peritonitis in patients on APD [32]. A more recent publication from Mexico including 237 patients, has reported a significantly lower peritonitis rate, in favor of APD [33]. In this trial, the relative risk for suffering the first peritonitis event was 0.68 in patients on APD compared to patients on CAPD. The above-mentioned meta-analysis of 2007 did not detect any differences between APD and CAPD in respect to relative risk, although APD was found to have significantly lower peritonitis rates compared to CAPD [10]. This meta-analysis was based on three randomized controlled trials, from which only two dealt with the issue of peritonitis and just one reported only three peritonitis episodes. Moreover, the results of this study

were virtually based on a clinical trial which included patients employing a cycler that had been abandoned [34] and thus should be interpreted cautiously [35]. Another prospective clinical trial from USA, from the late 80s', included 82 young patients and managed to demonstrate superiority of APD, with an approximately double risk for peritonitis events with CAPD, but still a similar incidence of exit site infections between both modalities [36].
A clinical trial including 132 pediatric patients in Turkey revealed a similar rate of peritonitis events between the two submodalities, but an increased peritonitis events rate caused by Gram-negative bacteria in children on APD [37]. In another study which analyzed data from 4247 patients from Canada, who had undergone PD from 1996 until 2005, a similar risk for peritonitis events was found between the two submodalities [38]. Another noteworthy recent clinical trial, including 508 cases of peritonitis in 205 patients, showed that APD was associated with prolonged duration of elevated leukocyte count in peritoneal dialysis fluid as well as longer duration of antibiotic treatment [39]**.** A prospective, multicenter clinical trial including 10 nephrological centers in Scotland, with follow-up period of 8 years, showed lower rates of peritonitis in patients on APD [40]. The authors commented that their results warrant cautious interpretation, considering the fact that patients on CAPD were older and that there were significant differences between the participating centers, such as the different peritonitis rates reported from the different centers, the small patient sample as well as the short follow-up period after the first peritonitis event. Finally, the utilization of the spike system for dialysis bag connection to the cycler in the USA instead of the safer Luer-lock connector used in Europe might play the most important role [41,42].

Intraperitoneal pressure-Patient compliance

The increased intraperitoneal pressure observed during the application of PD might lead to hernia formation and leakage of peritoneal fluid, causing discomfort in some patients. Performing the exchanges in the supine position, as occurs in APD, reduces the intraperitoneal pressure for more than 50% compared to the upright "full abdomen" position. The incidence of hernias is reported to be lower in patients on APD [16]; still this has not been confirmed by all trials [10]. Nevertheless, increased nighttime volumes and decreased daytime volumes (or even the preservation of an empty abdominal cavity during the day), might prove to be beneficial for patients unable to tolerate increased intra-abdominal pressure [43]. Thus, APD might be a satisfactory alternative solution to the surgical treatment of such hernias [6].
Patient compliance to the prescribed regimen is an important issue, since a considerable proportion of patients on PD do not comply with the treatment, with detrimental consequences to patient and technique survival [44]. The risk of inadequate compliance seems to be higher in patients on CAPD compared to those on APD, most probably due to the higher number of connections and disconnections needed in CAPD [45], as well as the discomfort associated with the increased intraabdominal pressure during CAPD [46].

Arterial blood pressure-Ultrafiltration and sodium clearance-Residual renal function

It is well-known that it is more difficult to achieve the ultrafiltration targets when the residual renal function declines. Existing data is not clear whether APD aids in achieving these targets. In a prospective study, including 53 patients on CAPD and 51 patients on APD, with a 10 month follow-up, ultrafiltration and sodium removal were lower in patients on APD than in their counterparts undergoing CAPD. Moreover, patients on CAPD demonstrated a better control of systolic blood pressure [47]. On the other hand, the EAPOS trial (European APD Outcome Study) enrolling 177 anuric patients undergoing APD demonstrated that more than 75% of patients achieved the ultrafiltration target of more than 750 mL/24h [48]. In a Canadian study including 56 patients on APD, with liberal icodextrin use during daytime dwells, blood pressure control was achieved in 93% of patients while volume control was independent of sodium removal [49]. Furthermore, recent data showed that fluid state and blood pressure control were not different between APD and CAPD, despite a higher daily sodium removal in CAPD patients [50]. A study from Korea, where 24-hour ambulatory blood pressure monitoring was performed in 26 patients on CAPD and 18 patients on APD, did not show any significant differences in blood pressure control and left ventricular hypertrophy in APD compared to CAPD [51]. A recent study from a Greek nephrological center enrolling 46 patients did not show any significant differences in sodium removal between patients on APD and CAPD, assuming appropriate utilization of icodextrin in both groups [52]. In conclusion, it appears that APD could be effective in achieving the targets of ultrafiltration and euvolemia despite the declining residual renal function, provided that prescribed clearance dose is adjusted accordingly [53].
The probability of a faster decline of residual renal function in patients on APD remains a subject of concern, especially regarding patients on NIPD. Although the results of the existing studies might be controversial, Marron *et al.* in their review report showed no statistically significant reduction of residual renal function in patients on APD [54]. Data from the NECOSAD trial demonstrated a higher risk of losing residual renal function in patients starting dialysis on APD compared to those starting on CAPD, especially during the first year [55]. Still this fact has not been confirmed in other recent publications [13,14] and both modalities appear to be equivalent.

Quality of life and sleep quality

APD appears to be superior compared to CAPD with respect to patient's quality of life; still all related published evidence is not definitive. In a multicenter study from the Netherlands investigators showed that patients on APD demonstrated better mental health, with lower levels of anxiety or depression compared to patients on CAPD during the same period of treatment. On the other hand, the physical aspects of quality of life were similar in both groups [56]. Another study from Denmark showed that patients on APD had significantly more time available for work, family, and social activities compared to those on CAPD. There was a tendency for less physical and emotional discomfort in the APD group, yet the difference was not significant [57]. In another interesting, although small study with regards to sample size, patients were allocated to CAPD treatment for 6 months and then they were shifted to APD therapy for the next 6 months. Patients showed improvement in parameters such as vitality, social functioning and mental health scores while being on APD; however this tendency was not significant [58]. More recent studies have not demonstrated any difference regarding the quality of life between the two methods [59-61]. A recent meta-analysis of 190 trials, all of them evaluating quality of life in end-stage CKD patients in relation to treatment modality, showed superiority of APD compared to CAPD, though not significant [62].
The issue of sleep disorders in patients on APD was studied in a randomized trial of Bro and associates, who showed that patients on APD demonstrated more sleep problems as compared to those on CAPD [57]. APD was also associated with a higher incidence of excessive daytime sleepiness [61]. Yet in another study, sleep quality was estimated as similar in both methods [59], whilst in another one, in which overnight polysomnography was performed in the patients enrolled, APD was associated with improved sleep quality and lower sleep apnea incidence, most probably due to better control of the hydration status during sleep [63].

APD in children and the elderly-assisted PD

In the United States approximately 95% of children with end-stage CKD, younger than 19 years old, undergo APD [2]. The same applies in Europe as well, for example in Italy [64]. Regarding the elderly patients on PD, APD is the prevalent modality of renal replacement treatment. In the USA more than 60% of PD patients over 65 years old, receive APD [2]. In this patient-group there is a greater need of assistance by a caregiver in order to perform the exchanges [65], a fact which might explain the increased use of APD, as it requires fewer connections.
Moreover APD has proved to be a reliable method of renal replacement treatment in patients older than 65 years. According to a study from the USA, technique failure and peritonitis rates in the elderly (>65 years old) patients on APD were not different compared to the younger patients. Additionally, quality of life measures were similar between all age groups [66].
APD plays a central role in the treatment of pediatric patients with end-stage CKD, especially infants. APD due to accurate determination of fill volume allows appropriate treatment individualization according to age, body size and growth- related metabolic needs [67]. Moreover, children on APD and their parents have more free time available during the day, as no exchanges are required during school time [68]. Compared to children on CAPD, children on APD showed lower peritonitis rates [68]. In another trial, enrolling more than 300 pediatric patients who were switched from CAPD to APD, results showed improved ultrafiltration, less edema, lower mean arterial blood pressure, improved peritonitis rates and fewer hospitalizations [69]. Another study from Hong-Kong reported impressing results with respect to quality of life of patients included. In this study, both children on APD (as well as their parents) and children who underwent renal transplantation and their parents seemed to experience similar quality of life [70].
A significant number of patients on PD need the assistance of a companion, nurse or caregiver in order to perform the exchanges. APD might be the modality of choice in these cases. APD requires only two connections and disconnections daily, which is an important advantage with regard to time saving. This diminishes the daily workload of the assistant and also might prove to be useful for patients who reside in nursing care institutions [25,71]. In another study from Denmark, 65 patients underwent assisted APD with satisfying results (54% two year survival and one episode of peritonitis in 26 patient-months), confirming the aforementioned results [72]. A recent observational trial from Brazil, enrolling elderly patients with physical or cognitive disabilities and lack of assistance as well as patients with lack of vascular access or hemodynamic instability during hemodialysis, showed that assisted APD is a reliable and effective homecare alternative for patients without other renal replacement therapy options [73].

When to apply APD

APD remains an alternative option for patients who are unable to achieve adequate clearance and ultrafiltration targets with CAPD. In such cases, an increased number of exchanges with CAPD leads to an impaired quality of life and might cause switching of dialysis modality to hemodialysis. Thus the application of APD with larger dwell volumes and longer nocturnal sessions, especially in combination with the use of icodextrin for the long dwell, or the addition of one daytime exchange (CCPD plus), could probably prolong technique survival. In slow transporters, a regimen with less frequent

exchanges during the night and probably the addition of one manual exchange during the day could be an alternative option.

Additionally, APD has been tried as a dialysis modality in patients who require urgent renal replacement therapy. The association of APD with lower intraperitoneal pressure might render the best option for immediate initiation of PD. In a retrospective study from Denmark, patients who initiated PD in less than 24 hours after peritoneal catheter insertion had a technique survival that was similar to that of patients who initiated APD on a scheduled basis [74]. In a prospective study from France, acute initiation of APD was an effective dialysis method [75], whilst it has been performed as a first-line emergent dialysis therapy as well, with satisfactory results [76].

APD and patient's employment and financial cost

In a study from Finland [77], similar employment rates were observed between patients on APD, those on home hemodialysis and transplanted patients, which ranged from 39-44%. Another study from Hong-Kong showed a statistically significant difference in the employment status of patients on APD compared to those on CAPD [78]. Thus, patients on APD had higher rates of full-time employment compared to those on CAPD (62.2% versus 15%). Moreover, a Spanish study concluded that APD, and to a lesser extent renal transplantation are the modalities of renal replacement treatment with the lowest impact on indirect costs due to morbidity, showing higher rates of employment than hemodialysis and requiring less disability benefits [79]. Another trial from the same research group demonstrated that the most active patients prefer APD as the initial modality of renal replacement therapy. Thus, approximately half of patients on APD are working, while approximately only one in five patients on hemodialysis are working [80]. Finally, according to a study from Mexico the annual direct medical cost per patient on PD increased from 15072 dollars in 2008 to 16452 dollars in 2010. The cost was higher for patients on APD compared to those on CAPD, although the difference was not statistically significant [81].

Conclusions

Automated PD is the most promising PD modality, with undoubtable advantages in patient's lifestyle. The possible clinical benefits of the method are still controversial and currently high peritoneal permeability remains the only strong indication for APD application. APD offers the advantage of choice and it can be more easily performed by employed patients, while offering more time for personal or family activities. It is suitable for children, elderly patients and patients who need assisted PD. APD should always be offered with respect to the patient's choice, which should not be overlooked during initiation of therapy [82]. Accepting (and application of) the patient's preference, regarding the modality of renal replacement therapy, has positive effects on quality of life [83], which is probably the most important criterion in the treatment of end-stage kidney disease.

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