Chapter 9

Cost-Effectiveness of Online Hemodiafiltration

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Additional information is available at the end of the chapter

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Abstract

Care of patients with end-stage renal disease (ESRD) is essential but also resource intense. We review several studies on online hemodiafiltration (OL-HDF), which concluded that high-volume OL-HDF is associated with better outcome compared to conventional hemodialysis. The cost-effectiveness of OL-HDF was shown in many studies. For example, in the Canadian setting of the Convective Transport Study (CONTRAST), the high-efficiency OL-HDF was shown to be cost-effective compared with low-flux hemodialysis (LF-HD) for patients with ESRD. In our study (Al Saran et al.), it was shown that the cost of hemodialysis was quite less in Saudi Arabia than in other industrialized countries while maintaining a high standard of care. In our retrospective analysis of the cost of OL-HDF in the same center, it was only 3% higher than the conventional HD, which indicates that it is cost-effective considering the improved hospitalization rate, the mortality rates, and the likely better quality of life associated with it. The trend of increased practice of OL-HDF may encourage the practice of home OL-HDF as well. It has been shown that home HD is more cost-effective than in-center HD and we presume that the same results will be applied to home OL-HDF as well.

Keywords: online hemodiafiltration, low-flux hemodialysis, middle molecules, cost

1. Introduction

Untreated end-stage renal disease (ESRD) carries a high mortality. The management of ESRD is either by dialysis or by a kidney transplant. Due to insufficient number of kidney donors in comparison with the progressive increase in the number of ESRD patients in need for dialysis,

dialysis remains the main modality of treatment. Since the care of patients with ESRD is resource intense, it is necessary to adopt measures that render the delivery of dialysis more cost-effective and improve the quality of care. The uremic syndrome is characterized by the accumulation of uremic toxins due to inadequate kidney function. The European Uremic Toxin Work Group has listed more than 90 compounds considered to be uremic toxins. Among them, 68 have a molecular weight less than 500 Da, 10 have between 500 and 12,000 Da, and 12 exceed 12,000 Da [1]. Solutes weighing less than 500 Da are considered low molecular weight solutes and they are removed by passive diffusion down a favorable concentration gradient. Urea is considered a marker of such toxins. Its clearance, as measured by Kt/V urea, correlates with patient morbidity showing the evidence that such toxins contribute to the uremic syndrome [2]. The mortality rate of patient on maintenance dialysis has been found to be 15–20% [3]. This is despite improvements in patient care and technology. In order to increase survival in dialysis patients, it was postulated in 1983 that increasing the Kt/V in conventional dialysis may help to reduce mortality. However, the hemodialysis (HEMO) study failed to show a positive effect on patient survival when dialysis dose per hemodialysis session was increased above the current K/DOQI recommendations [4]. Possible explanation for this unfavorable outcome could be in the kinetics of urea removal which is representative of small solutes, but not of larger-sized molecules such as middle molecules, large molecular weight proteins or protein-bound solutes, thereby making Kt/V misleading [5]. Clearance of urea accounts for only one-sixth of physiological clearance [1]. In addition, several shortcomings are associated with short dialysis schedules that are not captured by Kt/V index such as extracellular fluid volume control, phosphate control, and adequate removal of middle and larger uremic molecules compounds. Beta-2 microglobulin levels are associated with the development of dialysis-related amyloidosis and possibly reduced survival [6]. It seems likely that beta-2 microglobulin is a marker for overall-middle molecule clearance, including more toxic and yet unidentified uremic compounds [7–10]. Those solutes are better removed by high-flux membranes due to their more porous characteristics with increased permeability. Hemodialfiltration (HDF) is the treatment modality that combines diffusion and enhanced convection in order to facilitate removal of small molecular weight solutes. Moreover, small molecule removal is further increased with the use of high-volume OL-HDF. HDF is thus a more cardioprotective renal replacement therapy.

Recent randomized controlled trials (RCTs) have shown the survival advantage of HDF using high-convective volumes (23 L/session or 69 L/week prescription). In Peters et al.'s review [11] which is a pooled individual participant analysis of 4 RCTs, it was a observed that in patients receiving the higher delivered convection volume (>23 L per 1.73 m^2 body surface area (BSA) per session), the longest survival benefit was seen with **Hazard Ratio (HR)** of 0.69 (95% CI: 0.47; 1.00) for cardiovascular disease mortality and HR of 0.78 (95% CI: 0.62; 0.98) for all-cause mortality.

In another study by Canaud et al. [12], which was a retrospective data collection from over 2000 patients with a minimum follow-up of 2 years, the relative survival rate of OL-HDF patients was found to increase at about 55 **L**–75 **L**/week of convection volume.

2. Principles of hemodiafiltration

Ultrafiltrate volume is removed by the dialysis machine through increased transmembrane pressure (TMP), whereas the replacement solution is infused intravenously at equal volume minus the desired fluid volume removal to preserve extracellular fluid balance and isovolemic state. The replaced solution represents *substitution volume*, whereas convective volume represents the sum of substitution volume and desired fluid volume removal during the dialysis session. The fluid can be substituted either after the **dialyser** as the reference mode (post-dilution mode) or before the **dialyser** (pre-dilution mode) or the combination of both (mixed dilution mode).

3. Efficacy of online hemodiafiltration

Several studies have shown online hemodiafiltration (OL-HDF) to be superior to conventional hemodialysis in reducing all-cause mortality in hemodialysis patients. OL-HDF has been found to reduce cardiovascular events as compared with conventional hemodialysis.

Furthermore, OL-HDF has significantly improved patients' satisfaction and quality of life [13–16]. OL-HDF has also shown to be a cost-effective treatment for ESRD [17]. For example, in the prospective Convective Transport Study (CONTRAST), there was no significant difference between treatment groups with regard to all-cause mortality (121 versus 127 deaths per 1000 person-years in the OL-HDF and LF-HD groups, respectively); (hazard ratio, 0.95; 95% confidence interval, 0.75–1.20) after a mean follow-up of 3 years (range 0.4–6.6 years). Receiving high-volume hemodiafiltration during the trial was associated with lower all-cause mortality.

In the ESHOL multicentre, open-label RCT [14], patients on OL-HDF compared with those on HD had a 55% lower risk of infection-related mortality (HR, 0.45; 95% CI, 0.21–0.96; *P* = 0.03), a 33% lower risk of cardiovascular mortality (HR, 0.67; 95% CI, 0.44–1.02; *P* = 0.06), and a 30% lower risk of all-cause mortality (**HR**, 0.70; 95% confidence interval [95% CI], 0.53–0.92; P = 0.01). In conclusion, high-efficiency post-dilution OL-HDF reduces all-cause mortality compared with conventional hemodialysis. According to the Turkish OL-HF prospective RCT [15], 782 patients undergoing thrice-weekly HD were enrolled and randomly assigned in a 1:1 ratio to either postdilution OL-HDF or high-flux HD. Using a filtration volume of 17.2 ± 1.3 **L, there** was no difference in the primary outcome between the two groups (event-free survival of 77.6% in OL-HDF vs. 74.8% in the high-flux group, *P* = 0.28). Also, no difference was seen in the cardiovascular and overall survival, number of hypotensive episodes and hospitalization rate. However on further analysis, the patients who received higher substitution volume (>17.4 L per session) had better cardiovascular outcome (*P* = 0.002) and overall survival (*P* = 0.03) compared with those who received high-flux HD. The study of Karkar et al. [16] aimed to investigate the effect of OL-HDF versus high-flux HD (HF) on a patient's health-related satisfaction level. A higher satisfaction level was achieved by the OL-HDF group compared with HF group (*p* < 0.0001). In the OL-HDF group, there was less itching (9 ± 10 vs.

48 ± 10), less cramps (3 ± 5 vs. 55 ± 8), less joint pain and stiffness (24 ± 10 vs. 83 ± 8) with improvement in sexual performance (57 ± 10 vs. 5 ± 5), social activity (82 ± 9 vs. 15 ± 8), and general mood (94 ± 9 vs. 28 ± 16). High-efficiency postdilution online HDF versus high-flux HD significantly improved patients' satisfaction and quality of life, including social, physical, and professional activities.

4. Cost-effectiveness of OL-HDF

4.1. Review of the literature

In spite of the several studies which investigate the efficacy of OL-HDF, there were fewer studies which assessed the cost-effectiveness of this procedure. One of them was the CONTRAST [17] in which the cost-effectiveness of high-efficiency OL-HDF was compared with LF-HD for patients with ESRD based on the Canadian (Centre Hospitalier de l'Universite de Montreal) arm of a parallel-group RCT. Over a period of 74 months, an economic evaluation was conducted. To simulate costs and health benefits over lifetime, a Markov state transition model was constructed. A total of 130 patients were randomly allocated to OL-HDF (n = 67) and LF-HD (n = 63). The primary outcome was costs per quality-adjusted life-year (QALY) gained. The cost-utility ratio of OL-HDF versus LF-HD was Can$53,270 per QALY gained over lifetime, and it was fairly robust in the sensitivity analysis. It was concluded that in a Canadian setting, high-efficiency OL-HDF can be considered as a cost-effective treatment for ESRD.

In Mazairac et al. study [18], a cost-utility analysis was performed using a Markov model. It included data from the CONTRAST. Probabilistic sensitivity analyses were performed to study uncertainty, and costs were estimated using a societal perspective. Total annual costs for HDF and HD were €88,622 ± 19,272 and €86,086 ± 15,945, respectively (in 2009 euros). The incremental cost per quality-adjusted life year (QALY) of HDF versus HD was €287,679 when modeled over a 5-year period. Even under the most favorable assumptions like a high-convection volume (>20.3 L), this amount will not fall below €140,000 using sensitivity analyses. They concluded that HDF cannot be considered a cost-effective treatment for patients with end-stage renal disease at present. This was based on accepted societal willingness-to-pay thresholds.

Various factors may responsible for the true differences in the cost of dialysis provision between various studies. These factors may include variable standards of care, different management protocols, differences in the methodologies used, the older population of patients with more comorbid illness (especially in the United States), different import duties and shipping charges, local labor costs, dates of the studies, the differences in countries in which the analyses were carried out, nurse/patient and physician/patient ratios and the number of dialysis sessions. Direct comparisons may not be very informative. Finally, the comparison between countries in the cost of dialysis must take into consideration the morbidity and mortality outcomes in these patients, as well as perceived quality of life [19, 20].

We have previously [21] assessed the cost of hemodialysis according to the treatment protocols based on the current Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines. The

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cost data, which included direct and overhead costs, were analyzed during the period from 1 January 2007 to 30 June 2010. Direct cost included items related to dialysis treatment such as dialysis disposables, dialysis related drugs, medical personnel, outpatient medications, laboratory, and other ancillary survives.

The category	The cost/session		Percentage
(I) Direct cost	USD	SR	
(1) Dialysis disposables (including tubing, dialyzer, acid concentrate, needles, normal saline, dressing set, heparin and bed sheets)	40.53	152	13.64
(2) Medical equipments and maintenance	13.6	51	4.58
(3) The meals	7.12	26.7	2.40
(4) Personnel:			
a. Administrative	32	120	10.77
b. Medical	90.13	338	30.34
(5) Intravenous medications			
a. ESA	16.8	63	5.66
b. Vitamin D	1.06	4	0.36
c. Iron	0.8	3	0.27
d. Albumin and dextrose	0.53	2	0.18
(6) Vascular access creation and revision*	10.24	38.4	3.45
(7) Laboratory tests	10.19	38.2	3.43
(8) Imaging investigations	0.11	0.7	0.06
(9) Out-patient and crash cart medications	17.87	67	6
Total direct cost	241	904	81.15
(II) Indirect cost			
(1) Non-medical equipments with maintenance and housekeeping	15.55	58.3	5.23
(2) Medical records	0.5	1.86	0.17
(3) Building**	29	109	9.78
(4) Disposal of medical waste	0.71	2.66	0.24
(5) Meals for personnel	7.12	26.7	2.40
(6) Suit for personnel	0.22	0.83	0.07
(7) Automobile maintenance and fuel	1.28	4.8	0.43
(8) Utility bills (electricity, water and phone)	1.56	5.85	0.53
Total indirect cost	56	210	18.85
Total	297	1114	100

*Calculated based on the mean half-life of the access and on the mean frequency rate of re-insertion or revision.
**Calculated based on the current cost for the land and construction divided by 20 years for the construction and by 10 years for the land (investment rate).

Table 1. The unit cost of the categories associated with hemodialysis provision at the King Salman Center for kidney diseases.

Over head (indirect) cost included building, maintenance and engineering costs, housekeeping and administrative personnel. The mean total cost per HD session was calculated as 297 US dollars (USD) [1114 Saudi Riyals (SR)], and the mean total cost of dialysis per patient per year was 46,332 USD (173,784 SR). Out of the total cost, the direct cost was the major part (81.15%) (**Table 1**). The total cost was well below the average cost in the industrialized countries although a high standard of care was maintained.

The category	Hemodialysis	Hemodiafiltration
(I) Direct cost		
(1) Dialysis disposables (include tubing, dialyzer, acid concentrate, needles, normal saline, dressing set, heparin and bed sheets)	40.53	50.53
(2) Medical equipments and maintenance	13.6	13.6
(3) The meals	7.12	7.12
(4) Personnel		
a. Administrative	32	32
b. Medical	90.13	90.13
(5) Intravenous medications		
a. ESA	16.8	16.8
b. Vitamin D	1.06	1.06
c. Iron	0.8	0.8
d. Albumin and dextrose	0.53	0.53
(6) Vascular access creation and revision	10.24	10.24
(7) Laboratory tests	10.19	10.19
(8) Imaging investigations	0.11	0.11
(9) Out-patient and crash cart medications	17.87	17.87
Total direct cost	241	251
(II) Indirect cost		
(1) Nonmedical equipments with maintenance and housekeeping	15.55	15.55
(2) Medical records	0.5	0.5
(3) Building**	29	29
(4) Disposal of medical waste	0.71	0.71
(5) Meals for personnel	7.12	7.12
(6) Suit for personnel	0.22	0.22
(7) Automobile maintenance and fuel	1.28	1.28
(8) Utility bills (electricity, water, and phone)	1.56	1.56
Total indirect cost	56	56
Total	297	307

Table 2. Comparison of the cost/session between hemodialysis and hemodiafiltration in US dollar.

4.2. Retrospective comparison between HD and OL-HDF

In our retrospective analysis of the cost of OL-HDF in the same center, the cost of the OL-HDF was only 3.4% higher than the conventional HD (10 US dollar difference per session). This difference in cost was in the category of dialysis disposables (**Table 2**). It is attributed to (1) the cost of the water purification filter at the back of online HDF dialysis machine which cost an average of 1.95 USD/session, (2) the cost of tubing extension used for OL-HDF which cost 7.8 USD/session, (3) the cost of the treated water used as substitution fluid (its volume in our center was 30 L/session), which cost 0.25 USD/session. This little difference in the cost of water treatment between the two modalities may be attributed to the fact that we are using ultrapure water for the two modalities in order to minimize the risk of micro-inflammation associated with HD. We need to emphasize that in some centers that have the latest manufactured dialysis machine, there will be no extra cost for the tubing as it will be the same tubing in both modalities. Finally, there was no difference in the cost for using high-flux dialyzer as its price nowadays is almost the same as for low-flux dialyzer. In conclusion, this minor cost difference between HD and OL-HDF indicates that OL-HDF is cost-effective considering the advantages of the OL-HDF and the better quality of life associated with it. The possible presumed decrease in the cost of medications and hospitalization is another supportive factor for the cost-effectiveness of OL-HDF. In addition, OL-HDF may not be indicated for all the dialysis patients. In our center, OL-HDF was only performed for certain indications such as severe hyperphosphatemia, severe resistant hypertension, and resistant anemia.

4.3. The cost-effectiveness of home HD and home OL-HDF

The trend of increased practice of OL-HDF may encourage the practice of home OL-HDF as well. More intensive and/or frequent hemodialysis may provide clinical benefits to patients with ESRD; however, these dialysis treatments are more convenient to the patients if provided in their homes. It has been shown that home HD is more cost-effective than in-center HD, and we presume that the same results will be applied to home OL-HDF as well. In Komenda et al. [22] review of data from Australia, Canada, and the United Kingdom, it was noted that the cost of the first year for all hemodialysis modalities were higher than in subsequent years, and the cost for conventional home hemodialysis was lower than in-center hemodialysis in subsequent years. Their conclusions were similar to previous studies that home-based conventional and more frequent hemodialysis may provide clinical benefit at reasonable costs. In another study for Komenda et al. [23], they described a comprehensive funding model for a large centrally administered but locally delivered home hemodialysis program in British Columbia, Canada. There were 122 patients, of which 113 were still in the program at study end. In this two-year retrospective study, the majority of patients performed home nocturnal hemodialysis, and it was found that the total cost for home hemodialysis was higher in the first two years and it was lower by about 10,500 per year in the subsequent years. So their study explained a valid, comprehensive funding model delineating reliable cost estimates of starting as well as maintaining a large home-based hemodialysis program. Therefore, when designing budgets for home hemodialysis, consideration of hidden costs is important for administrators and planners.

McFarlane et al. [24] assessed the cost-effectiveness of home nocturnal hemodialysis (HNHD) in relative to in-center hemodialysis (IHD). In this Canadian one-year prospective study which was done at two centers in Toronto in the year 2000, HNHD had a higher mean number of treatments per week (5.7 vs. 3.0, $P = 0.004$). In the cost categories, staffing was found to be less expensive for HNHD (weekly $210 vs. $423, $P < 0.001$, PMA $4179 vs. $12,393). There was a trend toward lower costs for hospital procedures and admissions (weekly $23 vs. $134, $P = 0.355$, PMA $1173 vs. $6997), for the capital costs (weekly $118 vs. $17, $P < 0.001$, PMA $6139 vs. $871) and the cost of direct hemodialysis materials (weekly $318 vs. $126, $P < 0.001$, PMA $16,587 vs. $6575). On the other hand, there was a trend toward higher cost for laboratory tests (weekly $33 vs. $26, $P = 0.094$, PMA $1744 vs. $1364). Physician costs were the same at $128 per week (PMA $6650). The projected mean annual costs were more than $10,000 lower ($56,394 vs. $68,935). The weekly mean total cost for health care delivery was 20% less for HNHD ($1082 vs. $1322, $P = 0.006$). Their conclusion was that HNHD provides about three times as many treatment hours at nearly a one-fifth lower cost. The savings were evident even when only program and funding specific costs were considered.

5. Conclusion

OL-HDF seems to be cost-effective and much better than conventional hemodialysis for the patient's satisfaction, quality of life, patient's survival, dialysis-related mortality and morbidity, and cardiovascular outcomes. However, more prospective studies are needed on the cost-effectiveness of this procedure.

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