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ORIGINAL ARTICLE

Haemodiafiltration use in children: data from the Italian Pediatric Dialysis Registry

Fabio Paglialonga[1] · Enrico Vidal[2] · Carmine Pecoraro[3] · Isabella Guzzo[4] · Mario Giordano[5] · Bruno Gianoglio[6] · Ciro Corrado[7] · Rosa Roperto[8] · Ilse Ratsch[9] · Salvatore Luzio[10] · Luisa Murer[2] · Silvia Consolo[1] · Giovanni Pieri[1] · Giovanni Montini[1] · Alberto Edefonti[1] · Enrico Verrina[10]

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Abstract

Background High volume haemodiafiltration (HDF) is associated with better survival than conventional haemodialysis (HD) in adults, but data concerning its use in children are lacking. The aim of this study was to assess the prevalence of paediatric HDF use and its associated factors in recent years in Italy.

Methods We retrospectively reviewed the files of patients from the Italian Pediatric Dialysis Registry's database who were registered between January 1, 2004 and December 31, 2016 and treated with extracorporeal dialysis for at least 6 months, looking in particular at modality and its associated factors.

Results One hundred forty-one out of 198 patients were treated exclusively with bicarbonate HD (71.2%), 57 with HDF (28.8%). Patients treated with HDF were younger (median 9.7 vs 13.2 years, $p = 0.0008$), were less often incident patients (52.6% vs 75.9%, $p = 0.0031$), had longer duration of the HD cycle (26.9 vs 20.8 months, $p = 0.0036$) and had a longer time to renal transplantation (32 vs 25 months, $p = 0.0029$) than those treated with bicarbonate HD only. The percentage of patients treated with HDF increased with dialysis vintage (16.9% at 6 months, 38.1% after more than 2 years of dialysis). The use of HDF was stable over time and was more common in the largest centres.

Conclusions Over the observation period, HDF use in Italy has been limited to roughly a quarter of patients on extracorporeal dialysis, in particular to those with high dialysis vintage, younger age or a long expected waiting time to renal transplantation.

Keywords Extracorporeal dialysis · Children · Paediatric dialysis · Haemodiafiltration · Haemodialysis

Introduction

Notwithstanding the progressive improvement in the care of patients with end-stage renal disease (ESRD) over the last few decades, morbidity and mortality rates remain dramatically high, even in paediatric patients [1–5]. The need for an optimization of dialysis techniques and, in particular, for an improved dialytic solute removal, therefore, remains an absolute priority.

Conventional low-flux haemodialysis (HD) is a diffusive extracorporeal dialysis modality, which allows for the

✉ Fabio Paglialonga
fabio.paglialonga@policlinico.mi.it

1 Pediatric Nephrology, Dialysis and Transplant Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milan, Italy

2 Pediatric Nephrology, Dialysis and Transplant Unit, Department of Women's and Children's Health, University-Hospital, Padua, Italy

3 Nephrology and Dialysis Unit, Santobono Children's Hospital, Naples, Italy

4 Nephrology and Dialysis Unit, Department of Pediatrics, "Bambino Gesù" Children's Hospital-IRCCS, Rome, Italy

5 Nephrology Division and Dialysis Unit, Giovanni XXIII Children's Hospital, Bari, Italy

6 Nephrology Dialysis and Transplantation Unit, Regina Margherita University Hospital, Turin, Italy

7 Pediatric Nephrology and Dialysis Unit, Children's Hospital G. Di Cristina, Palermo, Italy

8 Nephrology and Dialysis Unit, Meyer Children's Hospital, Florence, Italy

9 University Department of Pediatrics, United Hospitals of Ancona, Ancona, Italy

10 Dialysis Unit, Paediatric Nephrology and Dialysis Department, G Gaslini Children Hospital, Genoa, Italy

effective removal of small uremic solutes, like urea. However, the optimization of small solute clearance is not associated with an improved survival of patients with ESRD [6, 7]. Haemodiafiltration (HDF) is an extracorporeal dialysis technique that uses a combination of diffusive and convective solute transport through a highly permeable membrane, thereby achieving a better clearance of middle and large molecular weight solutes than conventional bicarbonate HD [8, 9]. Since its introduction over 50 years ago, some technological developments, in particular the online production of ultrapure, sterile, pyrogen-free infusion fluids, have permitted this dialysis modality to gain progressively increasing attention and diffusion [9, 10].

Some adult randomized controlled trials and meta-analyses have recently demonstrated that high-volume HDF can lead to an improvement in all-cause and cardiovascular survival when compared to conventional HD, yet paediatric data in this field are scanty [11–19]. A few single-centre studies have shown that daily HDF is associated with significant benefits in terms of growth, cardiovascular status, phosphate control and inflammation, but in these trials, it is difficult to differentiate between the effect of convection and that of the intensified dialysis schedule [20–24]. A recent study has demonstrated that children switched from conventional HD to HDF showed, after 3 months of treatment, a significant improvement in terms of inflammation, antioxidant capacity and endothelial risk profile [25]. A paediatric prospective multicentre observational trial on this topic is currently ongoing [26, 27].

Given these data, it can be assumed that to date, the choice of any of the extracorporeal dialysis modalities in children has been largely guided by expert opinion and small trials, rather than by sound scientific evidence.

The aim of this retrospective study is to investigate the prevalence of HDF as treatment modality for children with ESRD in Italy and the factors correlated with the choice of this dialysis technique. Data were obtained from the Italian Pediatric Dialysis Registry over a period of more than 10 years.

Patients and methods

We retrospectively reviewed the files of patients from the Italian Pediatric Dialysis Registry (a permanent, nationwide chronic dialysis network of all 12 Italian paediatric dialysis units) who started extracorporeal dialysis before the age of 18 years between January 1, 2004 and December 31, 2016 and continued dialysis for at least 6 months.

The following data were collected at the beginning of the dialysis cycle and every 6 months thereafter:

- Patient age, primary kidney disease, comorbidities.
- Dialysis: modality (HD or HDF), number and duration of weekly sessions, membrane area and blood flow (Qb). HDF mode (pre, post, mixed) was not available from the registry database.
- Body weight and height, expressed as standard deviation scores (SDSs) using the general formula: $SDS = (x - x_i) / SD_i$, where x is the individual patient value, x_i the median value for the normal population and SD_i the standard deviation of the normal value. Body weight and height were normalized for chronological age, using the standards of the World Health Organization as references.
- Pre-dialysis systolic and diastolic blood pressure, expressed as SDSs.
- Residual urine output.
- Pre-dialysis blood urea, creatinine, haemoglobin, total protein, albumin, calcium, phosphate, bicarbonate, alkaline phosphatase, parathyroid hormone.
- Treatment with recombinant human erythropoietin (rhEPO).

Events including renal transplantation (rTx), death or switch to peritoneal dialysis (PD) were reported from the first day of treatment.

Statistical analysis

Patients were divided in two groups according to their dialysis modality: the conventional HD group (children treated with bicarbonate HD only) and the HDF group (those treated only with HDF or with both modalities). Treatment groups were studied using an "as-treated" analysis.

The data were expressed as median values and ranges, and statistically analysed using the Mann-Whitney test for continuous variables and the chi-squared test for dichotomous variables. Kaplan-Meier survival analysis was used to assess the time to death after initiation of dialysis treatment. Patients were censored at transplantation, when renal function recovered, when lost to follow-up or when reaching end of study period. A p value of < 0.05 was considered statistically significant.

Results

During the study period, 316 patients started chronic extracorporeal dialysis. After excluding patients older than 18 years, those treated with HD for less than 6 months and those treated with haemofiltration or acetate-free biofiltration, 198 paediatric patients were considered: 141 of them were treated exclusively with bicarbonate HD (71.2%) and 57 with HDF (28.8%). Among the HDF cohort, 36 children were treated exclusively by HDF, while 21 received both modalities.

The comparison between patients never treated with HDF (conventional HD group), and those who were treated with HDF (HDF group) is shown in Table 1. Patients treated with

Table 1 Comparison between patients treated with HDF and conventional HD (median values and interquartile ranges)

	HDF (*n* 57)	Conventional HD (*n* 141)	*p*
Age (years)	9.7 (3.3–13.5)	13.2 (9.8–15.1)	0.0008
Sex, females	23 (40.3%)	78 (55.3%)	0.14
Comorbidities	17 (29.8%)	33 (23.4%)	0.35
Primary kidney disease:			
CAKUT	26 (45.6%)	43 (30.5%)	0.24
FSGS	8 (14%)	18 (12.8%)	
Others	23 (40.4%)	80 (56.7%)	
Preceding treatment			
PD	16 (28,1%)	24 (17%)	0.0031
Conservative treatment	30 (52.6%)	107 (75.9%)	
rTx	11 (19.3%)	10 (7.1%)	
Duration of dialysis cycle (months)	26.9 (19.1–44.2)	20.8 (13.8–30.7)	0.0036
Outcome of dialysis cycle:			
Ongoing	5 (8.8%)	15 (10.6%)	0.042
Transferred to another centre	7 (12.3%)	13 (9.2%)	
Death	4 (7%)	2 (1.4%)	
Switch to PD	3 (5.3%)	2 (1.4%)	
Renal function recovery	0 (0%)	2 (1.4%)	
Deceased donor rTx	32 (56.1%)	102 (72.3%)	
Living donor rTx	6 (10.5%)	5 (3.5%)	

HDF haemodiafiltration, *HD* haemodialysis, *CAKUT* congenital abnormalities of the kidneys and urinary tract, *FSGS* focal segmental glomerulosclerosis, *PD* peritoneal dialysis, *rTx* renal transplantation

HDF were younger (median 9.7 vs 13.2 years, $p = 0.0008$), had more often switched from PD (28.1% vs 17%) or re-entered dialysis after a failed rTx (19.3 vs 7.1%) and were less often incident dialysis patients who had been on conservative treatment (52.6% vs 75.9%) than those treated with bicarbonate HD only ($p = 0.0031$).

Children within the HDF group had a longer dialysis vintage (26.9 vs 20.8 months, $p = 0.0036$) and a lower probability to terminate the cycle with a deceased donor rTx than those treated exclusively with bicarbonate HD (56.1 vs 72.3%; $p = 0.042$). Four out of 57 HDF patients and two out of 141 bicarbonate HD patients died during the dialysis period; however, a significant difference in overall survival was not observed ($p = 0.14$).

The median time to rTx was higher for HDF patients than for bicarbonate HD patients (32 vs 25 months, $p = 0.0029$, Fig. 1).

The probability of treatment with HDF was characterized by a significant centre effect, with the percentage of patients treated with HDF ranging from 13 to 75% in different units ($p = 0.0018$). In particular, HDF was used in 32.4% of the patients undergoing dialysis in the largest centres (those with more than 20 patients treated during the study period), but only in 18% of those treated in the smallest units, caring for less than 20 patients ($p = 0.044$).

The use of HDF was stable over time, HDF being used in 27.5% of the patients starting extracorporeal dialysis before 31 December 2010 and in 30.3% of those starting dialysis thereafter ($p = 0.66$). The use of HDF grew with the increasing dialysis vintage: in particular, the percentage of patients treated with HDF was 16.9% at 6 months and 38.1% after more than 2 years of chronic extracorporeal renal replacement therapy ($p = 0.0006$).

Data regarding dialysis schedule, biochemistry and anthropometry were collected over a median follow-up time of 14.3 months in 533 observations, of which 406 were in patients treated with bicarbonate HD and 127 in HDF patients (see Table 2): when compared with conventional HD patients,

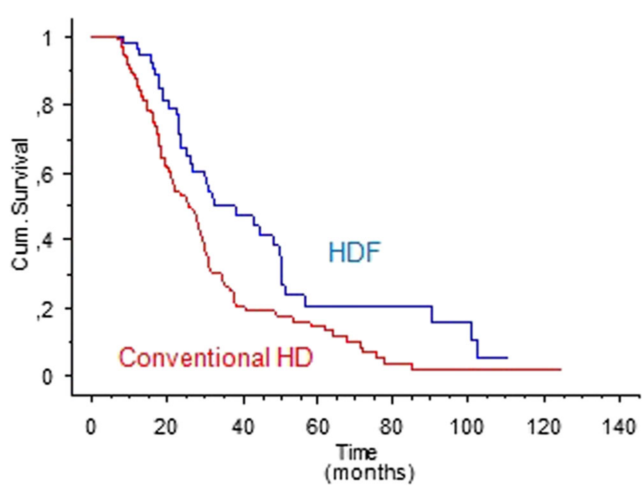

Fig. 1 Time to renal transplantation in patients treated with haemodiafiltration (HDF) and conventional haemodialysis (HD)

Table 2 Dialysis-related parameters and biochemical and anthropometric data during follow-up (median values and interquartile ranges)

	HDF *N* 127	Conventional HD *N* 406	*p*
N sessions/week	3 (3–4)	3 (3–3)	0.003
Session duration (hours)	3.5 (3.0–4.0)	4.0 (3.0–4.0)	0.07
Filter surface area/BSA (m^2/m^2)	1.0 (0.9–1.2)	1.1 (0.9–1.2)	0.231
Qb (ml/kg/min)	6.9 (5.8–8.1)	5.7 (4.8–7.3)	< 0.0001
Alkaline phosphatase (U/l)	200 (133–370)	205 (123–383)	0.89
Parathyroid hormone (pg/ml)	250 (95–517)	240 (106–486)	0.36
Serum protein (g/dl)	6.7 (6.3–7.0)	6.7 (6.2–7.3)	0.18
Serum albumin (g/dl)	4.2 (3.8–4.5)	4.1 (3.8–4.5)	0.28
Haemoglobin (g/dl)	10.6 (9.5–11.4)	11.0 (9.8–12.1)	0.007
Urea (mg/dl)	148.5 (91–168)	143 (99–175)	0.50
Serum creatinine (mg/dl)	9.5 (7.2–10.6)	9.0 (6.7–11.3)	0.93
Calcium (mg/dl)	9.6 (8.8–10.1)	9.6 (9.0–10.0)	0.61
Phosphorus (mg/dl)	5.4 (4.5–6.6)	5.5 (4.5–6.6)	0.84
Bicarbonate (mEq/l)	21.7 (19.8–23.4)	22 (19.2–24.0)	0.61
Urine output (ml/kg/day)	0 (0–9.0)	0.3 (0–13.7)	0.08
rhEPO dosage (U/kg/week)	240 (146.5–405)	190 (106–300)	0.014
Weight SDS	− 1.3 (− 2.0; − 0.7)	− 1.3 (− 1.8; − 0.7)	0.30
Height SDS	− 2.0 (− 3.1; − 1.0)	− 1.8 (− 2.7; − 1.0)	0.46
SBP SDS	1.5 (0.4–2.4)	1.9 (0.7–3.0)	0.06
DBP SDS	1.3 (0.7–1.8)	1.2 (0.4–2.0)	0.73

HDF haemodiafiltration, *HD* haemodialysis, *BSA* body surface area, *rhEPO* recombinant human erythropoietin, *SDS* standard deviation score, *SBP* pre-HD systolic blood pressure, *DBP* pre-HD diastolic blood pressure

those in the HDF group received more dialysis sessions per week and had a higher Qb. They also had a significantly higher erythropoietin dose but lower haemoglobin levels. Systolic blood pressure levels were lower in the HDF group than in the conventional HD group, but in a non-statistically significant way. Urine output was not significantly different between the two groups.

Discussion

The main finding of this study is that the use of HDF in Italy over the last few years has been limited to almost 25% of paediatric patients on extracorporeal dialysis and, in particular, to the youngest patients and to those with the longest dialysis vintage. Moreover, patients treated with HDF were less often incident patients and had longer transplant waiting times than those treated with conventional HD only.

These results should be viewed in the light of the available literature. Haemodiafiltration was proposed some decades ago to improve the removal of small and middle-sized uremic toxins by combining diffusion and convection. The possibility of producing a virtually unlimited amount of sterile, pyrogen-free fluid has progressively increased the availability of online HDF in adult and paediatric dialysis units [9, 10, 28].

Many studies of adult patients over the last 20 years have clearly demonstrated that HDF allows for a higher clearance of middle molecular weight toxins, such as ß2-microglobulin, an increased removal of phosphate and a better prevention of intradialytic hypotension compared to conventional HD [29–33]. Only recently, three large randomized controlled trials in different European countries have compared the survival rates of patients treated with conventional HD and HDF. Neither the CONTRAST study nor the Turkish online HDF study showed significant survival differences between the two groups, but a survival advantage was demonstrated for HDF patients receiving high convective volumes in both studies [11, 12]. The ESHOL trial compared conventional HD with high-efficiency HDF (mean convective volume 23.7 l/session) in 906 adults and demonstrated a significant improvement in survival with HDF [13]. Four recent meta-analyses have basically confirmed this finding [14–17]. In particular, Mostovaya et al. showed that high-volume online HDF was associated with a decreased risk of all-cause and cardiovascular mortality of 16 and 27%, respectively, as compared to conventional HD [17]. Although the first paediatric experiences with HDF were published many years ago, paediatric data in the literature remains at best scarce [28]. A few reports have highlighted some significant clinical benefits associated with the use of daily HDF in children, but it is impossible to distinguish between the benefits which are due to the convective modality and those which are secondary to the higher frequency of treatment [20–25]. Ağbaş et al. switched 22 children from conventional HD to HDF and showed that after 3 months of HDF treatment, there was a significant reduction in ß2-microglobulin, markers of inflammation and oxidative stress compared to HD [25]. A prospective multicentre observational trial, the Hemodiafiltration, Heart and Height (3H) Study, is currently ongoing and aims at assessing the benefits of HDF on the cardiovascular risk profile, growth and nutrition, compared to conventional HD in children [26, 27].

As our study investigated the prevalence of HDF use over a 13-year period, starting from 2004, it can be easily assumed that the choice of dialysis modality during this period was not influenced by the most recent trials, which have provided the most convincing evidence in support of the superiority of HDF over conventional HD. On the other hand, the problem of cost should also be considered, as high-flux membranes and large volumes of ultrapure water add additional costs to the treatment. Taking all these factors into consideration, it is not surprising that in Italy, the use of HDF to treat children with ESRD was restricted to a subgroup of patients only and, in particular, to patients with a long dialysis history or a foreseeable long period on dialysis, as it can be assumed that this population carries the highest risk of accumulating significant comorbidities due to middle molecular weight toxins. Even the higher prevalence of HDF in small children can be interpreted under this perspective, as small children often have longer transplantation waiting times and an expected long dialysis history. The use of HDF in young children might also be explained with the better dialysis tolerance of this technique compared with conventional HD, which could be particularly worthwhile in patients at high risk of intradialytic morbidity [32, 33].

Very few data exist about the prevalence of HDF use in paediatrics. A recent survey conducted among 51 paediatric dialysis units across Europe showed that 47% of units performed HDF, which was reserved for 37% of children on extracorporeal dialysis, a slightly higher percentage than that found in this study [34]. In the abovementioned survey, the main obstacles to performing HDF were a lack of appropriate dialysis machines (74%) and/or ultrapure water (63%), no trained staff (5%) and costs (32%) [34]. Although not formally assessed, looking specifically at the Italian situation, it can be hypothesized that, among these factors, economic concerns and maybe an overestimation of the actual costs of the procedure could have been the major obstacles to the diffusion of HDF in Italy.

Given this scenario, it is not surprising that the prevalence of HDF use in Italy has remained rather stable over a long period of time, almost unaffected by the technological advancements in dialysis machines which have made the implementation of this HD modality easier. Interestingly, HDF was more often prescribed in large centres than in the small ones, which can maybe be interpreted as being secondary to better expertise or to the fewer financial constraints seen in the largest units. When looking at these data, the peculiarity of the Italian setting should be taken into account, and in particular the lack of national or local recommendations concerning the indications for the different dialytic procedures. It should also be considered that other options for children on extracorporeal dialysis without an immediate perspective of renal transplantation are almost absent in Italy, with daily HD or HDF being practiced in selected cases only and with no paediatric centres performing home HD or HDF.

The analysis of the effects of different dialysis modalities was beyond the scope of this study. More importantly, the comparison of the outcomes of patients treated with HDF and those on conventional HD was biased, due to the significant differences between the two groups, in particular as far as age is concerned. It is, for example, self-explanatory that HDF patients, who were younger than those treated with conventional HD, had lower haemoglobin levels despite receiving higher rhEpo dosages and received more sessions per week, as these are obviously strictly age-dependent parameters. The relatively low number of observations, collected at different time intervals, makes it difficult to overcome this bias using a multivariate analysis. The same is true for phosphate: the lack of a significant difference in serum phosphate between the two groups should be interpreted in the context of the study limitations, given that the superiority of HDF over conventional HD in phosphate removal has been demonstrated in large trials [31]. With these concerns in mind, some preliminary hypotheses might be drawn, but they will need to be confirmed by future trials. It may be of note that serum creatinine was almost identical in the two groups, despite the significant differences in age, dialysis schedule and blood flow: as creatinine is mainly dependent on muscle mass and clearance, from a purely theoretical point of view, these data might be a possible sign of a better nutritional status in children with HDF, which would be in line with some preliminary findings from recent paediatric studies [20, 22, 25]. In the same way, HDF patients had a lower systolic blood pressure compared to the conventional HD group, although the difference was not statistically significant: this finding needs to be confirmed in the future; however, it would be in line with some published reports [27]. Of course, all these considerations should be viewed as hypotheses only, needing confirmation in further trials.

The results of our study should be viewed with caution, as they could be hampered by the many methodological limitations typical of a multicentre, registry-based study. Among them, one major limitation is the absence of data concerning the convective volume, as the adult literature is unequivocal in highlighting that the survival advantage of patients treated with HDF is significantly correlated with the convective dose. Given that one of the possible benefits of HDF over HD could be a more effective prevention of cardiovascular complications, it could have been interesting to look at some cardiovascular parameters, such as left ventricular mass index, that were unfortunately not available in the registry. The same is true for some biochemical parameters, such as β2-microglobulin, which could have confirmed the superiority of HDF over HD in the clearance of middle-sized molecules, and for other clinical parameters, such as inflammatory markers and intradialytic events, that are supposed to be influenced by HDF.

Notwithstanding these limitations and to the best of our knowledge, this study is the first to provide a well-documented picture of the use of HDF in an industrialized country over a long period of time. Nowadays, these data could be of particular interest, as the large adult trials and meta-analyses published over the last few years, and the ongoing 3H study too, will soon change the prevalence of HDF use in the paediatric population.

Conclusions

According to data from the Italian Registry of Pediatric Dialysis, HDF use in Italy over the observation period has been limited to roughly a quarter of patients on extracorporeal dialysis, particularly those with a high dialysis vintage, young age or a long expected waiting time until renal transplantation. It will be interesting to see how the final results of the 3H study will help us to better understand the true benefits of HDF in paediatrics and to assess over time the impact of the ongoing scientific evidence on the dialysis prescription practice in children with ESRD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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