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Original Article

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The outcome of chronic dialysis in infants and toddlers—advantages and drawbacks of haemodialysis

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Abstract

Background. Improvements in dialysis technology allow replacement therapy for even the youngest of children with end stage renal disease. Nevertheless, the cumulative experience in this age group is limited.

Methods. We compared the outcome of 20 children who initiated chronic dialysis before the age of 1 year (weight 4.9 ± 2 kg, Group 1), with a particular focus on those under the age of 1 month (eight children, weight 2.9 ± 0.34), to that of 14 patients, aged 1.1–3 years when starting dialysis (weight 10.1 ± 1.7, Group 2).

Results. The outcome was poor in the youngest age group; only 3/8 survived to 3 years. Of those who started dialysis between the ages of 0.3 and 3 years, 84% underwent kidney transplantation. The survival of 1-, 3-, 5- and 8-year-old patients was 96%, 88%, 84% and 84% respectively. Severe co-morbidities were present in almost half of those who died. Hospital stay was 3.5 times longer in Group 1 than in Group 2 during the first 3 months of dialysis. Permanent central venous catheters inserted under ultrasound guidance resulted in a 4.4-fold increase in catheter survival compared to non-cuffed catheters. Marked blood loss at beginning of haemodialysis (HD) is attributable to residual volume in the dialysis system (15.7 mL/kg/month) and frequent blood tests (12.1 ± 5.9 mL/kg/month). These values decreased 2-fold after 8 months of treatment.

Conclusions. The main factors determining the poor outcome of infants on dialysis are extremely young age at initiation and severe co-morbidities. Despite some disadvantages, HD may be successfully implemented in infants and toddlers, in highly specialized centres with a well-trained nursing staff.

Keywords: ESRD; haemodialysis; infants; outcome; peritoneal dialysis; toddlers

Introduction

The experience of treating neonates and infants with end-stage renal disease (ESRD) by dialysis, and particularly by haemodialysis (HD), is limited. It is technically difficult, labour intensive and requires a highly qualified nursing staff. Peritoneal dialysis (PD) at this age group has its own difficulties including frequent episodes of catheter malfunction and the risk of severe infections. It may take 1–2 years of dialysis treatment in order for the patient to achieve a body weight of 9 kg, when successful kidney transplantation can be performed. Because of the generally poor outcome, an ethical dilemma arises whenever a newborn or an infant presents with ESRD. Initiating chronic dialysis in infancy is still considered inappropriate by many paediatric nephrologists [1].

PD is considered as the preferred method of renal replacement therapy (RRT) in young children. HD accounts for 3–14% of ESRD treatment in infants and young children, according to several studies [2–9]. However, in cases where PD is contraindicated, fails or is inappropriate because of psychosocial problems, HD remains the only alternative treatment. Over the last decade there has been a significant improvement in HD techniques due to the improved technology of the dialysis machines and central venous catheters, as well as the miniaturization of filters and circuits. These factors may favourably affect the outcome of HD in infancy.

During the period 1993–2004, 20 infants under the age of 1 year (eight of whom were <1 month of age) and 14 toddlers aged 1–3 years initiated chronic dialysis in our unit.

The aim of this study was twofold: (1) to assess the outcome and duration of hospital stay of infants who began chronic dialysis during their first year of life, in comparison with children who started dialysis at 1–3 years of age, and (2) to analyse several issues unique to HD treatment in

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infants and toddlers, including vascular access and anaemia due to blood loss.

Subjects and methods

Medical records of all patients who started chronic dialysis in the Pediatric Nephrology Unit of Shaare Zedek Medical Center, Jerusalem, Israel between April 1993 and December 2005 were retrospectively evaluated. The staff of physicians and nurses during this time period remained relatively constant.

The outcome was assessed in 20 infants (Group 1), who started dialysis before the age of 12 months and in 14 children (Group 2), who initiated dialysis between the ages of 13 and 36 months. We compared these groups with respect to the following outcome measures: duration of dialysis treatment (HD and/or PD) until end-point, number of patients who died during dialysis, duration of RRT [which included time period on dialysis and after kidney transplantation (Tx)] until end-point, percentage of patients who died on RRT, Kaplan–Meier survival on RRT and growth assessed as standard deviation scores (SDS) for weight and height. The end-point for time period on dialysis treatment was death, December 2005 or first kidney Tx, and for RRT death or December 2005.

The following data were also collected for analysis of outcome: age and weight at initiation of dialysis and at end-point or at kidney Tx, medical diagnoses (underlying kidney disease and co-morbidities), causes of death and ethnic background. Height and weight SDS were calculated at initiation of dialysis and at 6-month intervals until Tx, at 1, 2 and 3 years following renal Tx and compared by the paired *t*-test. Only those children who were treated with dialysis for >6 months were included in this part of the analysis. Three infants with profound psychomotor retardation were excluded.

Additional data were collected according to the following categories: (1) duration of in-hospital stay (expressed in patient-months) and (2) for children treated by HD, type of vascular access and survival rate of central venous catheters.

The extent of blood loss was evaluated in eight infants who were treated with HD for a minimum of 6 months (mean 22.2 $\pm$ 4.4 months, range 6–27 months) during the years 2003–2004. For this purpose we determined (1) the residual blood volume (RBV) in the dialysis system following a dialysis session and (2) the amount of blood drawn for blood tests and blood admixture in 'dead space' of central venous lines.

RBV was determined by rinsing the dialysis filter and tubing with normal saline three times (until it appeared clean), centrifugation of the rinsing fluid and measurement of the erythrocyte volume. RBV was calculated based on the haematocrit of the patient measured at the beginning of the corresponding dialysis session. This procedure was performed twice in each patient. The second assessment was performed after measures had been taken to minimize RBV by increasing heparin dose and carefully rinsing the system with saline before disconnecting the patient from the dialysis machine. Full washout of the dialysis system is impossible in infants without infusing large volumes of fluids per body weight.

The amount of blood drawn for tests was determined by counting the number of blood analyses registered in the hospital computer database for each patient during the time period on chronic HD. The total amount of blood was calculated according to the preset volume of test tubes (mostly microtainers) used for various tests: blood chemistry (0.5 mL), CBC (0.5 mL), blood type and crossmatch (0.5 mL), antibiotics blood levels (0.5 mL), venous blood gases (0.5 mL), blood cultures (2.5 mL), PTH and ferritin (3 mL).

The initial doses of erythropoietin (Recormon, Roche), expressed in units/kg/week, as well as the maximal doses, were recorded. Recormon was administered intravenously. Only intravenous iron supplementation (iron sucrose) was used in HD patients in order to maintain a serum ferritin level of 150–300 mg/dL (not exceeding 500 mg/dL) and transferrin saturation over 20%. The number of packed red blood cells (pRBC) transfusions (10 mL/kg per transfusion) and that of the use of priming with pRBC, which equals the extracorporeal volume of the HD system, were also noted. Patients with haemolytic anaemia were excluded from this part of the study.

HD management

Most of our young patients were predominantly treated by HD and we therefore focus on this modality. HD for newborns, as well as initial HD sessions for infants, was usually performed in the paediatric intensive care unit. The HD machines used were Centry 3 until 2004, or Gambro AK 200/AK200S after that time. In recent years, the Fresenius dialysers and Gambro tubing systems have been used (minimal priming volume: 58 mL). The maximal extracorporeal volume (ECV) allowed was 10% of total blood volume (calculated as 80 mL/kg body weight). When the sum of dialyser and tubing system volumes exceeded this amount (body weight <7 kg), priming of the system initially with pRBC (diluted with saline to haematocrit of 40%) and subsequently priming with 5% albumin or normal saline was implemented. All infants weighing <5 kg required priming with pRBC for longer periods, depending on haemoglobin concentration and intradialytic haemodynamic stability. If serum haemoglobin concentration was below 10 g/dL in these infants, one-third of the volume of the HD system was slowly transfused to the patient at the end of, or preferably, during the session. Mannitol (or 20% albumin in cases of hypoalbuminaemia) was often administered to maintain intravascular volume to prevent intra-dialytic hypotensive episodes and to avoid disequilibrium syndrome. Weight was recorded before and after each dialysis session. Blood pressure was measured at least every 30 min.

A major effort was made to achieve adequate nutritional status and growth in all patients. In order to provide sufficient calorie and protein intake, most children were fed via nasogastric or gastrostomy tubes. In oliguric or anuric patients, concentrated formula (Similac 60/40, Abbott Laboratories, made with less water: 9 g per 40 (100 kcal/100 mL) or 50 mL (80 kcal/100 mL) with added nutrients was used, in order to comply with fluid limitations. It should be noted that concentrating the formula increases the caloric intake in decreased volumes, but results in increased potassium concentrations. Non-concentrated

Table 1. Characteristics of infants and small children on renal replacement therapy

	Group 1	Group 2
Weight at initiating dialysis (kg)[a]	4.9 ± 2	10.1 ± 1.7
Duration of dialysis (month)[a]	20.7 ± 12.1	14.1 ± 11.1
Duration of PD (month)[a]	14.0 ± 13.7	7.5 ± 3.2
Duration of HD (month)[a]	15.4 ± 9.9	8.6 ± 6.6
Duration of RRT (month)[a]	45.6 ± 41.6	76.8 ± 46.8
Started with PD	16	4
Started with HD	4	10
Predominantly on HD/PD	11/9	11/14
Girls/boys	10/10	7/7
Jewish/Arab families	10/10	6/8
Etiology of ESRF:		
Renal dysplasia/hypoplasia[b]	7	3
Diffuse mesangial sclerosis	4	7
Renal vein thrombosis	2	0
Familial haemolytic-uremic syndrome	2	0
Primary hyperoxaluria	2	0
Ischaemic lesion	2	0
Others[c]	1	4

[a]Mean ± SD.
[b]Renal dysplasia/hypoplasia was a part of Prune belly syndrome in two children, of Kabuki syndrome in one.
Group 1: patients who started dialysis before 1 year of age. Group 2: patients who started dialysis at the age of 1–3 years. RRT: renal replacement therapy (dialysis or dialysis with subsequent period after kidney transplantation); PD: peritoneal dialysis; HD: haemodialysis; ESRF: end-stage renal failure.
[c]Others: Group 1: interstitial nephritis in 1; Group 2: nephronophthisis in 1, congenital nephrotic syndrome of Finnish type (after bilateral nephrectomy) in 1, focal segmental glomerulosclerosis in 1, bilateral Wilms tumour in 1.

formula contains 13.8 mEq/L of potassium, whereas the 100 kcal preparation contains 20.7 mEq/L. Almost all anuric infants required polystyrene resin (Kayexalate) to control serum potassium concentrations. As all infants weighing <5 kg in our study were severely oliguric or anuric, they required four weekly dialysis sessions once they stabilized. Suboptimal compliance with fluid restrictions was another indication for four weekly dialytic treatments even for older children or those who had moderate urine output. None of our patients received less than three weekly treatments.

A paediatric nephrologist examined all patients at least once a week. Plasma electrolytes, BUN, creatinine, calcium, phosphate and CBC were checked weekly, whereas full biochemical profile, intact parathyroid hormone (PTH), ferritin, transferrin saturation and venous blood gases were assessed monthly. In the patients with inadequate response to treatment with vitamin D metabolites, PTH was measured every 2 weeks. All patients were followed by a dietitian and were seen by a paediatric endocrinologist every 3 months. Patients who were fed via a gastrostomy or jejunostomy tube were monitored by a paediatric gastroenterologist. Over the last 4 years the families were also followed by the unit's psychologist.

Dialysis adequacy was assessed monthly, by calculating Kt/V and URR in all patients. Every patient was discussed at monthly multi-disciplinary staff meetings.

Results

Dialysis treatment was offered to all neonates and infants with ESRD, unless they were <2.4 kg in weight or had life-threatening co-morbidities.

Before initiating dialysis treatment all parents were informed about ESRD management in infancy and its possible complications and outcomes. Parents were offered the option to refuse treatment when severe co-morbidities existed. None refused dialysis treatment or asked to withdraw therapy. This included one family who had a previous child who succumbed to primary hyperoxaluria (PH1) while being treated with chronic HD. Many families sought advice from a religious authority prior to making their decision. Minimal duration of dialysis treatment was 2 months (mean 18.7 ± 16.2, range 2–51).

Among children who initiated dialysis during infancy (Group 1) the most frequent cause of renal failure was renal dysplasia/hypoplasia (7/20) whereas in Group 2 it was diffuse mesangial sclerosis (7/14, Table 1). Significant co-morbidities were more frequent in patients of Group 1 compared with Group 2. In four children of Group 1, ESRD was part of a systemic disease [2 PH1, 2 familial haemolytic-uremic syndrome (HUS)] and in three additional patients it was associated with malformations in other organ systems (Kabuki syndrome, anoxic brain damage, hydrocephalus with blindness). Prune belly syndrome and cardiac defects were present in onepatient of each group, whereas brain infarct and sensory-neural deafness in another, both of Group 2. At the beginning of chronic dialysis nine children of Group 1 were anuric (or severely oliguric), eight were moderately oliguric and only three were polyuric, whereas in Group 2, eight were anuric, four moderately oliguric and two polyuric.

Most children in both groups were treated with HD (Table 1). Sixteen children from Group 1 were initially treated with PD (some of them following a brief period of urgent HD). Subsequently, nine of them were switched to HD due to PD failure (Table 1). Of note, four of these nine children were transferred to our HD unit from other paediatric nephrology centres when PD failed. Only four children of Group 2 started on PD, all of whom were transferred later to HD. The remaining children were treated by HD all along mainly because of significant psycho-social problems in their families, or at the request of their parents. The number of children of Jewish or Arab descent was comparable in both groups (Table 1).

Duration of dialysis treatment until the first kidney Tx was longer in Group 1 (26.6 ± 7.6 months, 9 children) compared to Group 2 (15.6 ± 12.0 months, 13 children, $P = 0.02$). Among the children of Group 1 who died, the mean period of dialysis treatment before death was 18.7 ± 16.2 months (range 2–51 months). For three patients who continued dialysis until December 2005, this period was 26.6 ± 2.3 months.

Outcome

Significantly more children in Group 1, compared to Group 2, died while treated with dialysis ($P < 0.05$, Table 2). The first group was subdivided into two subgroups: those who

Table 2. Outcome of renal replacement therapy in infants and toddlers

	Group 1[a]	Group 2[a]	*P*
Number of patients	20	14	
Died while on dialysis	8 (40%)	1 (7.1%)	<0.05
Continue dialysis	3 (15%)	0 (0)	
Underwent kidney Tx	9 (45%)	13 (92.8%)	<0.01
Died after Tx[b]	2 (10%)	0	
Died while on RRT[c]	10 (50%)	1 (7.1%)	<0.02
Alive	10 (50%)	13 (92.8%)	<0.02

[a]Group 1: infants who started dialysis under the age of 1 year; Group 2: children who started dialysis at the age of 1–3 years.
[b]One patient died after kidney–liver Tx.
[c]RRT: renal replacement therapy (dialysis or on dialysis with subsequent period after kidney Tx).

started dialysis during their first month of life and those who began dialysis between 3 and 12 months of age. There were no patients who started dialysis between the ages of 1 and 3 months.

The outcome was particularly poor in patients who initiated dialysis during their first month of life (eight patients; mean weight 2.9 ± 0.34 kg, range 2.4–3.4 kg): five of eight patients died with ESRD and one following kidney Tx. The difference between the outcome of the youngest subgroup and those who initiated dialysis between 3 and 12 months (12 children; mean weight 6.5 ± 1.2, range 4.5–8.5 kg) did not reach statistical significance. However, the outcome was significantly poorer when compared with Group 2 ($P = 0.01$) and with all children aged 3–36 months taken together ($P < 0.02$, Table 2).

During the study period only 1 of 8 patients of the youngest subgroup underwent kidney Tx, compared to 8 of 12 children of the 3–12 months subgroup ($P < 0.05$) and 13 of 14 patients of Group 2 ($P < 0.01$). Only one patient of the youngest subgroup and one of the 3–12 months subgroup died after Tx (both within 1 month) whereas all other children who underwent renal Tx are alive.

The mean duration on RRT (including time on dialysis and following renal Tx) in children of Group 1 was 45.6 ± 41.6 months: for those who survived to December 2005 it was 67.7 ± 45.1 months (range 25–149), and 21.0 ± 15.5 months for those who died (range 2–51 months). In Group 2, the duration of RRT was 76.8 ± 46.8 months.

Among eight patients who began dialysis during the first month of life, five survived >1 year and only three >3 years (two of them are currently on dialysis, Figure 1). By contrast, 24 of 25 (96%) children for whom chronic dialysis was initiated above the age of 1 month, survived at 1 year of RRT, 22 of 25 (88%) at 3 years, and 21 of 25 (84%) at 5, 8 and 10 years (15 patients were followed over 5 years and 6 over 10 years).

Only one child from Group 1, who has been on dialysis for 34 months, was not considered a candidate for kidney Tx, because of severe respiratory problems and profound psychomotor delay. One of 9 transplantations performed in patients of Group 1 and 4 of 13 of Group 2 were living related Txs (LRTx). Seven additional parents from both groups expressed their wish to donate a kidney. Five of them recanted over time, and two children died before Tx.

Causes of death

Of the 11 deaths in our cohort, only 1 was related to the dialytic treatment. The latter was a sudden death shortly after initiation of the procedure and may have resulted from air embolus or massive stroke. In the remaining cases, the causes of death were not directly related to complications of dialysis. Two patients (both of the youngest subgroup, on PD) died from culture negative hyperpyrexia. One patient (Group 2), who was left at home unattended, died due to hyperkalaemia resulting from drinking fruit juice. In five children death was attributed to severe co-morbidities or systemic diseases: PH1 with multi-organ involvement [1], severe pulmonary hypertension, caused by structural anomaly of the pulmonary vasculature [1], and suspected peritonitis in a child with severe hydrocephalus and profound psychomotor delay. The remaining two died after Tx: one child from severe cardiovascular co-morbidity and the other, with factor H deficiency familial HUS, due to RSV pneumonitis following combined kidney-liver Tx. One child died from necrotizing enterocolitis. One patient from Group 1 who had PH1 was transferred to another hospital and died of unknown cause. Of the eight patients from both groups who died while on dialysis in our unit: five were on PD and three on HD.

Growth

Individual height and weight SDS curves during dialysis period and following renal Tx are depicted in Figure 2. Mean height SDS did not change significantly following 6, 12 and 18 months of dialysis treatment of children in Group 1 compared with initial values, or in children of Group 2 at 6 and 12 months (Figure 3). Deviation of height and weight did not differ significantly between children of Groups 1 and 2 at initiation of dialysis and following 6 and 12 months of treatment (Figure 3A and B). In Group 1 there was a significant weight gain during the first 6 months of treatment expressed as a decrease in SDS ($P = 0.008$, Figure 3B). This was due to the marked increase in weight ($P < 0.01$) in those with severe initial weight deficit (under −3.0 SDS; mean −5.0 ± 1.5). In children with initial SDS above −3.0 (mean −1.8 ± 0.8) there was no significant weight gain ($P = 0.3$). This difference was also observed in Group 2 ($P = 0.03$) but to a lesser extent (Figure 2C and D). The weight SDS remained constant among children of Group 1 after the first 6 months (Figure 3B). There was no difference in height and weight changes between patients on PD and HD during the first 6 months of dialysis (height: +0.09 ± 1.4 versus +0.01 ± 0.7; weight: −0.28 ± 1.2 versus −0.1 ± 1.0, respectively). Growth hormone (GH) was used in eight children of both groups during HD therapy, all of whom were over 1 year of age. The difference in mean ΔSDS per year, evaluated at least 6 months prior

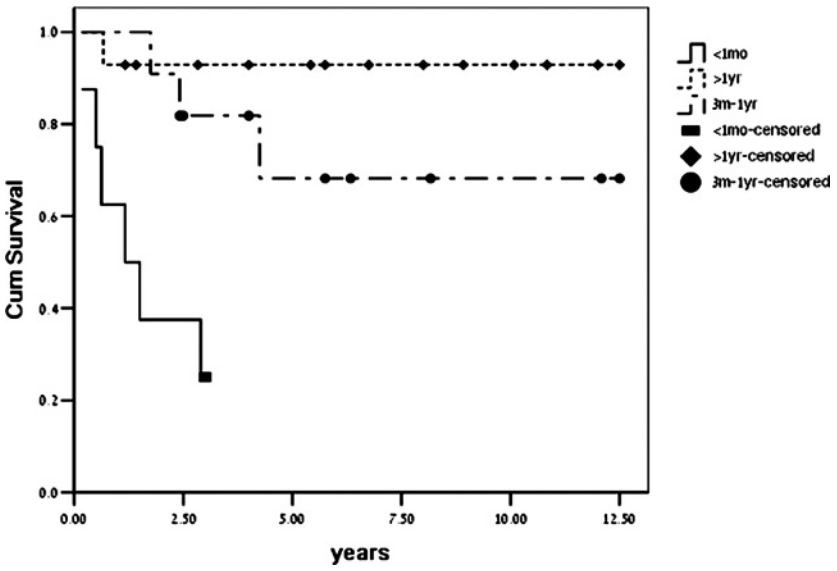

Fig. 1. Kaplan–Meyer survival curves for children on renal replacement therapy, started dialysis under the age of 1 month, at the age of 0.3–1 year and at the age of 1.1–3 years. Survival in Subgroup 1 (<1 month) was significantly lower ($P = 0.007$) compared to Subgroup 2 (3–12 months) and Group 2 (13–36 months; $P < 0.001$).

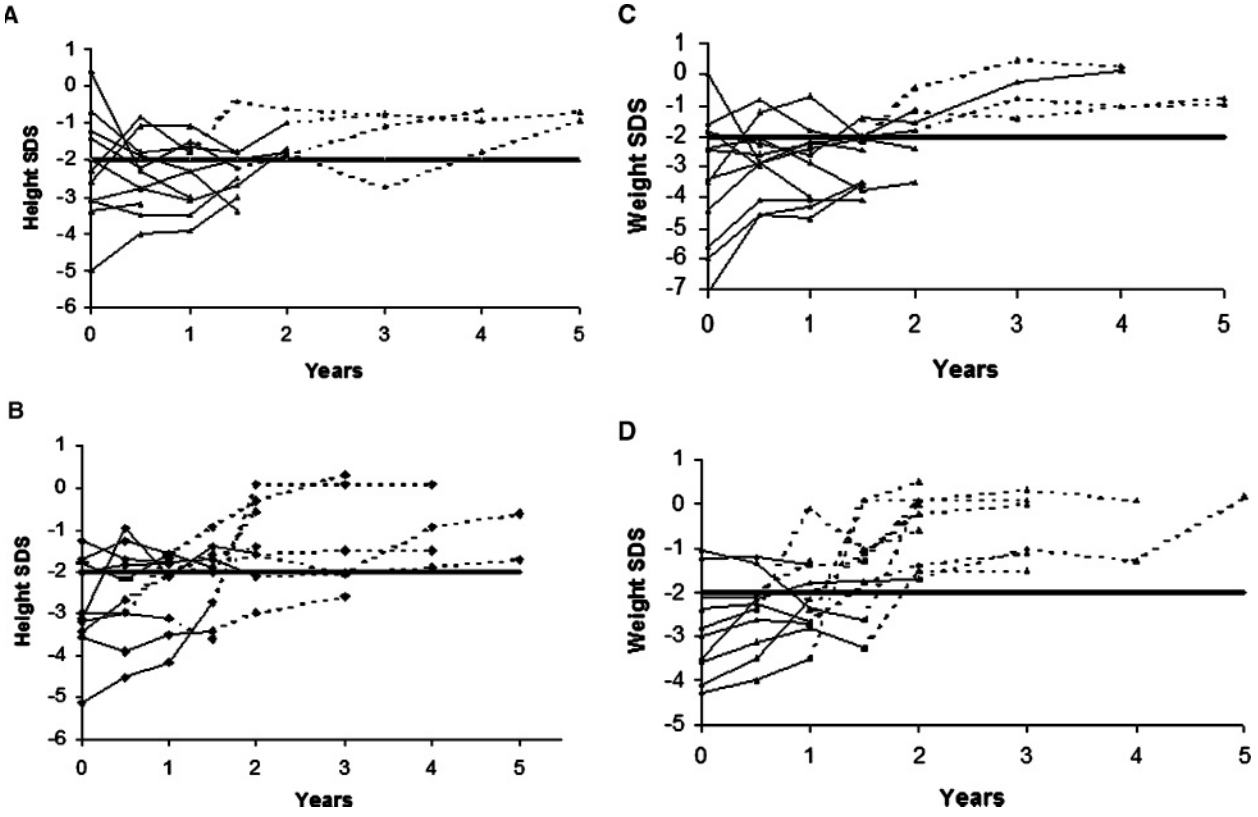

Fig. 2. Height and weight standard deviation scores (SDS) individual curves in infants and toddlers treated with dialysis and following kidney Tx. Height SDS in Groups 1 and 2 (**A** and **B**, respectively) and weight SDS in the corresponding groups (**C** and **D**) were calculated at the initiation of dialysis, 0.5, 1, 1.5, 2 years of dialytic therapy (solid line) and 1, 2 and 3 years following renal Tx (dotted line).

to initiation of GH and during therapy, was not significant (-0.3 ± 1.3 and $+0.55 \pm 0.5$).

An increase in weight was seen 1 year following renal Tx ($P < 0.01$), whereas height gain was only detected at 2 ($P < 0.01$) and 3 years ($P < 0.01$) after Tx (Figure 3C).

Hospital stay

All children were hospitalized for the initiation of chronic dialysis. Most of the infants weighing <5 kg and those who had ESRD complications (pulmonary oedema or severe electrolyte imbalance) or severe co-morbidities were

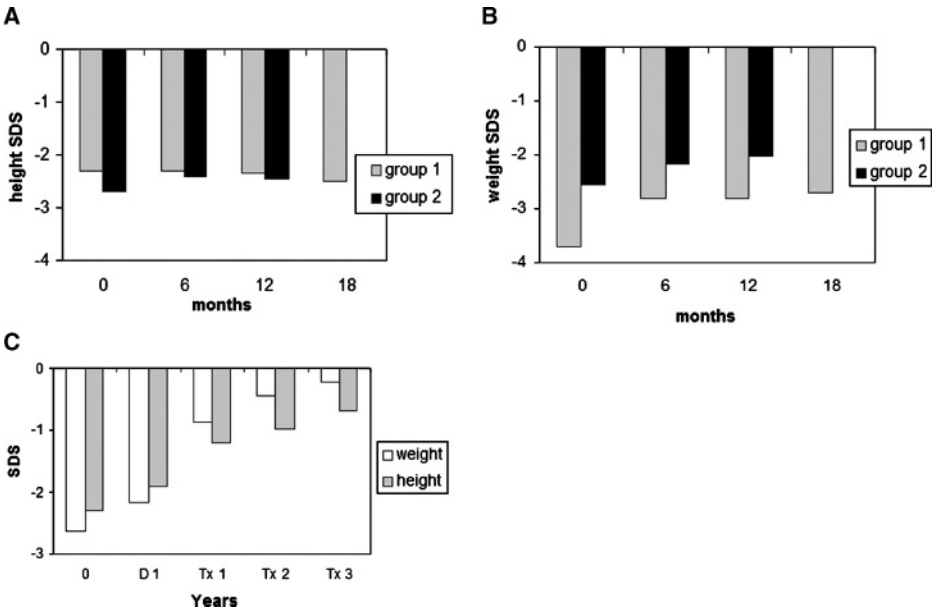

Fig. 3. Mean SDS for height (**A**) and weight (**B**) in infants and toddlers with ESRD treated with dialysis and following kidney transplantation (**C**). The *x*-axis shows the time from start of dialysis. Comparison of mean SDS while on dialysis (1 year after initiation) and following transplantation was performed for children of both groups together (**C**). This analysis included children who had been treated with dialysis for at least 1 year and followed over 3 years after renal Tx.

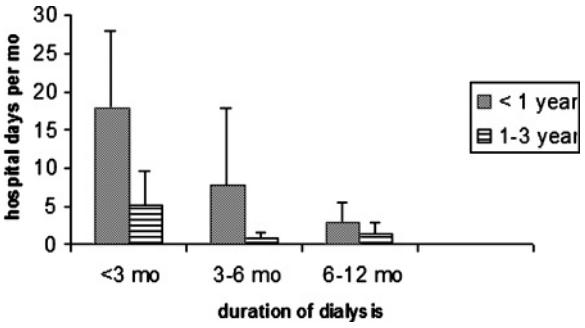

Fig. 4. Hospital stay (days per month) in infants and small children treated by dialysis. Hospital stay was significantly longer in patients of Group 1 compared to Group 2 during the first 3 months of dialysis treatment ($P < 0.001$), some longer ($P = 0.05$) after 3 months and was similar ($P > 0.05$) in both groups after 6 months of dialysis. In each group the duration of hospitalization was longer in the first 3 months of dialysis compared to the period of 3–6 months ($P < 0.02$ and $P < 0.01$ for Group 1 and Group 2) and 6–12 months ($P < 0.001$ and $P = 0.01$, respectively) of dialysis treatment.

admitted to the paediatric intensive care unit. The hospital stay of infants was particularly long during the first 3 months of dialysis treatment (17.9 ± 10 days per month, Figure 4). This was especially true for those who began treatment during the neonatal period (24.1 ± 7.3 days/month). The duration of hospitalization was significantly shorter in Group 2 during the first 3 months ($P < 0.001$) and tended to be shorter during the subsequent 3 months of HD treatment ($P = 0.05$, Figure 4). There was no significant difference in hospital stay between children treated by HD or PD (data not shown).

Vascular access for HD

All children from Group 1 were dialysed through a central venous line (CVL) placed in the internal jugular vein. Since 2000, all CVLs were cuffed and tunnelled permanent catheters (Medcomp 8F/18 cm) inserted under ultrasound and fluoroscopic guidance by interventional radiologists in the angiography suite. This technique bore no complications except for mild bleeding at the exit site, shortly after the procedure. In children of Group 2, HD was performed either via CVL (permanent catheters, as above, since 2000) or an arteriovenous (A-V) fistula (seven patients). The lines were filled between dialysis sessions with the exact volume of heparin (1250–5000 units/mL), according to the catheter size. The mean survival rate of permanent catheters was much higher compared to acute (non-cuffed) catheters (5.7 ± 2.2 months versus 1.3 ± 0.8 months, respectively). The main reasons for CVL removal were malfunctioning due to thrombosis or malposition, or persistent bacteraemia despite appropriate antibiotics treatment, including interdialytic filling of the catheter with antibiotics ('antibiotic lock'). When catheter thrombosis was suspected, urokinase was administered prior to considering catheter removal.

Arteriovenous (A-V) fistulas (one native and three grafts) were created in four children who were under the age of 3 years at the time of surgery who weighed 8.7 ± 0.46 kg (8.2–9.5) and in three patients (two native and one graft) between 3 and 4 years of age who weighed 13.2 ± 0.76 kg (12.2–14 kg). All AVFs were created by the same vascular surgeon. The anastomoses in the native A-V fistulas were between the cephalic vein and brachial or radial artery (in one each) and transposed basilic vein to the ulnar artery in one toddler. In the other four children an A-V graft (polytetrafluoro-ethylene) was used for anastomosis

between the axillary or cephalic vein and the radial, ulnar or brachial arteries. Fistulas matured 2–3 months following surgery. The exact puncture site was determined by duplex evaluation prior to its first use. For the first three to four HD sessions, a single needle was inserted into the AVF and was used in combination with one port of the CVL. There were three episodes of graft obstruction that required surgical reconstruction. Fistulas closed spontaneously in all children following renal transplantation.

Blood loss in HD patients

The mean RBV in the HD system was found to be 8.2 ± 2.0 mL per session. Efforts made to minimize blood loss included: increasing the heparin dose (controlled by ACT measurements) and meticulously rinsing the tubing with normal saline at the end of each dialysis session. This resulted in the decrease of the mean RBV to 7.2 ± 3.6 mL per session or 78 mL per month per patient. In the patients of Group 1, the minimal RBV was equal to 15.7 mL/kg/month during the first month of chronic HD treatment.

The amount of blood drawn for tests and 'dead space' during the first month of HD treatment was 12.1 ± 5.9 mL/kg/month. Total blood loss was 27 mL/kg/month (Figure 5). The RBV, as well as the amount of blood drawn for tests, expressed per kilogram of body weight (Figure 5), decreased with time primarily because of weight gain. As the general medical condition stabilized, significantly less blood tests were drawn. Eight months following the initiation of dialysis treatment blood loss decreased to approximately half of the initial amount.

Treatment of anaemia

This consisted of intravenous erythropoietin and iron supplementation as well as blood transfusions whenever needed to replace blood loss. The amount of blood transfused to patients of Group 1 during the first 3 months of HD treatment was 25 ± 17 mL/kg/month (2.5 blood transfusions per month). This volume decreased gradually to 6 ± 5 mL/kg/month after 6 months ($P < 0.02$) and to 2 ± 2 mL/kg/month (equivalent to one transfusion in 5 months) after 1 year of HD treatment ($P < 0.01$). The amount of blood transfused to the children of Group 2 was lower compared to Group 1 during the first 3 months of dialysis treatment (7.4 ± 5.7; $P = 0.02$) and did not differ significantly in subsequent months (2.2 ± 3.0 and 1.6 ± 2.2 mL/kg/month after 3–6 and 6–12 months of HD treatment, respectively). The initial erythropoietin dose in Group 1 was 230.6 ± 84.3 (range 147–366) units/kg/week with a mean maximal dose of 876 ± 262.0 9 (range 340–1252) units/kg/week.

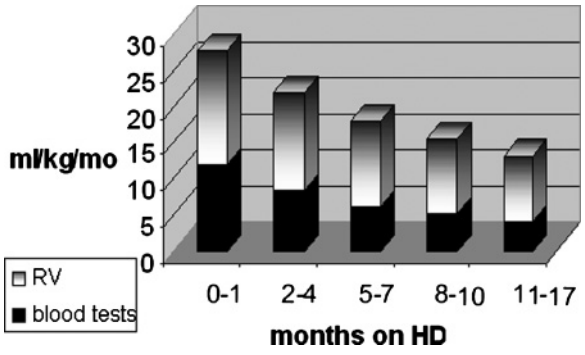

Fig. 5. Blood loss in infants and small children on haemodialysis (mL/kg/month). RV—residual blood volume in the haemodialysis system.

Discussion

In our experience, the outcome of infants who start dialysis during the neonatal period is poor. Prognosis was significantly better in children who initiated dialysis after the age of 3 months and especially after their first year of life. Most of these children underwent successful kidney Tx.

Young age at initiation of dialysis has been previously shown to be a significant predictor of poor outcome with increased risk of death. Groothoff *et al*. [10] found the mortality rate among children who reached RRT before the age of 5 years to be 2.7 times greater than that of to older children. In the 2003 NAPRTCS cohort [6], the mortality rate reported in infants (13.6) was six times higher than in adolescents (2.2). In the study of 192 patients from Britain and Ireland who reached ESRD before 2 years of age, 14% died because dialysis treatment was withdrawn or never started and 27% died while receiving dialysis [11]. Mortality was 45% among those whose dialysis was initiated prior to 1 month of age. More recently Shroff *et al*. [8] reported that 6 out of 21 children (28.6%) who started dialysis under the age of 1 year died before the age of 5 years. In the most recent (2007) NAPRTCS study [9] there was no difference in mortality between patients starting dialysis during the neonatal period (24%) and those who initiated dialysis at the age of 2–24 months (20%). In our study, the mortality among children who initiated dialysis during their first month of life was higher than that reported by the American and British groups. The rate was 3.8 times that of children who started dialysis between 3 and 12 months and 8.8 times higher than those who initiated RRT at 13–36 months of age. Only three out of eight patients who started chronic dialysis during the newborn period survived beyond 3 years, whereas in those who started RRT at 3–36 months the 3-, 5- and 8-year survival was 88%, 84% and 84% respectively. High mortality rate among the youngest children in our study could be explained by the increased prevalence of co-morbidities. Also, enrolling patients who had been on dialysis for at least 2 months excluded from the analysis those children who had reversible renal failure. Finally, all our families opted for their children with ESRD to undergo chronic dialysis.

Improvement in the outcome of RRT in infants and small children in recent years has been demonstrated in several publications. These studies were based both on large multicentre registries, such as the NAPRTCS study [5,6,9], the Dutch cohort study [10], the UK Renal Registry [11], EDTA study [12], or on the experience of a single centre, such as that of Great Ormond Street Hospital for children in London [8,13,14]. Nevertheless, the cumulative experience of treating the youngest children with ESRF is still limited.

No single cause of death could be identified in our study nor in the studies of Shroff *et al*. [8,14]. Wood *et al*. [5]

and Coulthard *et al*. [11] reported that most children died of infection. Heart diseases, including cardiac arrest, hypertensive heart failure and pericarditis, were found to be responsible for 31% of deaths in the report of Ehrich *et al*. [12]. In several studies [8,13–15], the high mortality rate in infants on RRT was attributed to severe co-morbidities. Almost half of our patients who started dialysis during their first year of life had significant co-morbidities or systemic diseases. Death was attributed to severe co-morbidities in half of the non-survivors: in one-third of those who composed the youngest age group (<1 month) and in all those who died from the 3–12 months old subgroup. Culture negative hyperpyrexia was the cause of death in two additional children of the youngest age group, both treated with PD. This phenomenon has only once previously been described. Hyperpyrexia with heat stroke was the cause of death in 1 of 51 non-survivors aged 0–5 years at initiation of dialysis in a study of Wood *et al*. [5]. An additional child from our cohort who has severe brain damage and has been treated with HD, following a brief period of PD, has experienced recurrent culture negative episodes of hyperthermia (41°C) during his first 2 years of life.

Poor prognosis coupled with the enormous emotional burden for the families charged with the care of their child pose an ethical dilemma when a paediatric nephrologist has to decide whether chronic dialysis should be initiated in a newborn. There are no established guidelines that address this issue. Of 192 children from the United Kingdom, who reached ESRF before the age of 2 years, 15 (7.8%) were not treated [11]. A multinational survey of paediatric nephrologists conducted by Geary in 1998 [1] revealed disparate opinions among paediatric nephrologists regarding the appropriateness of starting RRT in young infants. We offered dialysis to all infants with ESRD weighing over 2.4 kg without life-threatening co-morbidities. Despite our belief that parents of the youngest children who have severe co-morbidities are free to decide not to start RRT, there was not one family who refused dialysis or asked for withdrawal later. The decision of parents is obviously influenced by the medical team's attitude. Most parents follow physician's advice, but the decision of religious families was primarily based on the ruling of religious authorities.

It is sometimes difficult to evaluate the severity of co-morbidities at a very young age when dialysis is initiated. In such cases the ethical dilemma may only surface later. One of two patients of the youngest age group, who is currently still on dialysis, has anoxic brain damage involving the brain stem, leading to severe respiratory problems as well as profound developmental delay. When he reached the weight of 9.5 kg, his mother wished to donate her kidney. Given his severe mental retardation and the co-morbidities, which render his chance of surviving transplantation slim, we advised her not to do so. She did though request for dialysis to be continued. This was the only child in our cohort who has never been a candidate for Tx (3.8% of all children who reached the weight of 9 kg).

It is difficult to achieve adequate growth in infants and toddlers undergoing chronic dialysis, especially those with co-morbidities. In the majority, height and weight at the start of dialysis was >2 SD below the mean. Mean deviation from normal height (SDS) remained stable during dialysis treatment in both groups. More children of Group 1 had severe weight deficit at the beginning of dialysis and they experienced significant weight gain during the first 6 months of treatment resulting in a decrease in mean SDS. Our results are in accordance with those reported by the Great Ormond Street Hospital Group [8,14]. A previous report from the same hospital describing young children treated by PD only demonstrated better growth [13]. The relative contribution of GH therapy was difficult to assess due the small number of patients and a number of confounding factors including co-morbidities, infections and non-compliance. Marked improvement in growth was seen following renal Tx.

Among patients in our study who initiated dialysis during their first year of life, the mean time to kidney Tx was 2.2 years. The waiting period was primarily determined by the time until a weight of 9 kg was achieved. In Group 2 the waiting time was shorter (1.3 years). The percentage of LRTxs was comparable in both groups and was therefore not a factor in the prolonged waiting time for transplantation in Group 1. A similar waiting period was reported by the NAPRTCS registry [6]: 2.1 years for children who started dialysis under the age of 2 years.

In contrast to the common practice of implementing PD in young children with ESRD, we treated most young children with HD. Since 1998, 18 out of 21 patients who initiated dialysis during their first 3 years of life were predominantly on HD. The majority of these children had their RRT switched to HD because of PD failure (almost half of them were referred from other centres). In five cases HD was the initial choice because of marked psychological problems or socio-economic difficulties. Parents of six additional children, whose weights were 7–8 kg, chose HD as they planned to donate a kidney shortly after starting dialysis. Three of them donated a kidney 2–4 months following initiation of HD. The remaining three parents changed their mind, but did not wish to switch treatment to PD.

The outcome of infants and young children undergoing HD was not worse than of those on PD: five of eight patients who died while on dialysis were treated by PD. There was no significant difference in growth, during the first 6 months of treatment or hospital stay between patients on HD or PD. Analysis of the outcome of small children, treated by PD [13] or by HD [14] in Great Ormond Street Hospital in London, showed similar mortality (4/20 and 4/18, correspondingly). Thus, the option of HD should be considered for treatment of infants and toddlers with ESRD.

The quality of HD treatment of young children in our unit has improved remarkably over the last few years. First, only permanent central venous catheters are used, and they are inserted under ultrasound and fluoroscopic guidance by invasive radiologists. This technique has simplified the procedure, reduced the complication rate and resulted in a significant increase in catheter survival rate.

Notwithstanding some previous success in the creation of arteriovenous fistulas in toddlers (four of whom were <3 years of age with a weight range of 8.7–9.5 kg), the use of permanent CVLs is generally preferred. Another

improvement over the 12-year period was in the quality of the nursing care. As the number of children under 3 years of age increased (at one point representing over one half of all dialysis patients) the nurses gained more experience in treating this unique group of patients. Of note, we also instituted a psychologist-guided support group solely for the parents of these young children. The preponderance of young children in our care also prompted us to introduce art, music and animal therapy as well as medical clowns to our unit. One of the advantages of HD is that it relieves parents of some of the responsibilities and burden in the care of the child and obligates closer medical supervision (at least thrice weekly).

Even with a highly experienced nursing staff there are still some drawbacks to HD treatment in infants. There is a need for closer haemodynamic monitoring, especially towards the end of the session. Furthermore, higher blood loss (adjusted for body weight) was noted in HD patients, which was attributed to residual volume in the dialysis system and to frequent blood tests. Blood loss due to surgical procedures or rare occurrences of clotting in the dialysis system was not recorded. The amount of blood loss may therefore be underestimated. Residual volume in the HD system that was found to be as high as 15.7 mL/kg/month at the beginning of treatment, gradually decreased with time. Anaemia was corrected with high EPO doses, iron supplement and occasionally with blood transfusions. High EPO dosing was the preferred approach, as it has no adverse impact on future transplantation. The EPO doses used were higher than those recommended for children with chronic kidney diseases [16–21], but are commonly used for treatment of anaemia of prematurity [22–25] and in cancer patients on chemotherapy [26,27]. None of our patients required evaluation for pure red cell aplasia [28,29] as they all responded to EPO therapy. In most cases the EPO dose required decreased with time, and it was discontinued following successful Tx. None had symptoms of EPO overdose [30], nor were there side effects.

In conclusion, the main factors determining the poor outcome of infants with ESRD on dialysis are extremely young age (<1 month) at initiation and severe co-morbidities. The available data does not permit establishing clear criteria regarding for which, if any, infants dialysis should be withheld, as potential for long-term survival exists in almost every child. HD may be successfully implemented in infants and toddlers with ESRD, as long as there is a well trained nursing staff and comprehensive supportive services.

Conflict of interest statement. None declared.

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