Renal Transplant Thrombosis in Children

By A.F. van Lieburg, M.C.J.W. de Jong, A.J. Hoitsma, F.G.M. Buskens, C.H. Schröder, and L.A.H. Monnens
Nijmegen, The Netherlands

● **Data concerning 100 consecutive renal transplantations in children were analyzed to determine factors enhancing the risk of renal transplant thrombosis. The incidence of renal transplant thrombosis was high, at 12%. It is concluded that in addition to young age and low body weight of recipient and young age of the donor, also a high preoperative urine production contributes to the occurrence of thrombosis. Children with hypoplastic or dysplastic kidneys are at greater risk for thrombosis. Considering the influence of high urine production of the native kidneys, it may be possible to prevent thrombosis by albumin and ample fluid administration.**

INDEX WORDS: Renal transplant thrombosis, risk factors, prevention.

THROMBOSIS of the transplanted kidney is an important cause of early graft failure in children. A multicenter review concerning 1,045 renal transplants in children found that 22.5% of all graft failures occurring in the first 60 days after transplantation were caused by thrombosis.[1] A variety of risk factors has been described (Table 1), including some that can account for the fact that this complication has become mainly a pediatric problem.[1-20] The influence of young age of recipient and donor has been emphasized especially. Another condition that has been associated with renal transplant thrombosis in children is high urine production of the native kidneys, causing intravascular volume depletion.[1,2] Until now this factor has received relatively little attention. Because management of thrombosis depends on prevention, all predisposing factors need to be regarded. The goal of this study is to evaluate risk factors for thrombosis in a group of 100 pediatric transplantations.

MATERIALS AND METHODS

Data concerning 100 renal transplantations in children, performed between 1977 and 1990 in the St Radboud University Hospital in Nijmegen, were collected retrospectively.

A standard surgical technique was used. All grafts were placed retroperitoneally in the contralateral iliac fossa. The graft vessels were anastomosed, using a running suture, with arteria and vena iliaca communis or arteria and vena iliaca externa of the recipient, depending on the size and length of the vessels and length of the ureter. Until 1983 immunosuppression was achieved with prednisone and azathioprine. Since then, instead of azathioprine, cyclosporine has been used. Initial doses of cyclosporine consisted of 3 or 5 mg/kg per 24 hours intravenously, followed by 15 or 18 mg/kg per 24 hours orally after 48 hours. Perioperative fluid management: during surgery 2.5 L saline-glucose solution was given per 1.73 m^2 body surface area. In addition, since 1983, mannitol solution 20% was administered in a dosage of 250 mL per 1.73 m^2 body surface area, and since 1989 children weighing less than 18 kg received 20 mL albumin solution 10% per hour during the first 2 hours of the operation. Blood pressure was kept at a level considered appropriate for the particular child. Postoperatively, saline-glucose solution was given in an amount of 1 L per 1.73 m^2 body surface area plus diuresis every 24 hours.

Thrombosis was diagnosed on clinical (cessation of urine production, signs of thrombosis in the homolateral lower extremity) and radiological (radionuclide scan, arteriography) findings and subsequently confirmed at surgical exploration and histological examination.

Factors that, according to the literature, predispose to transplant thrombosis were analyzed (Table 1). For statistical calculations, the Wilcoxon test, χ^2 test, and Pearson correlation test were used where appropriate. Significance was accepted for a P value of less than .05.

RESULTS

Eighty-one children received 93 postmortem donor transplants (PMD) and 7 living related donor transplants (LRD). Eighty-one underwent the procedure for the first, 16 for the second, and 3 for the third time. All patients except 1 had been on hemodialysis or peritoneal dialysis with a mean duration of 18.6 months (SD 14.1).

In 12 recipients, thrombosis of the allograft with subsequent graft loss occurred. In 4 patients, the obstruction was located in the renal artery, and in 7 patients in the renal vein. In 1 patient the site of thrombosis was uncertain because of late transplantectomy of a necrotic kidney. This was the only patient in which on histological examination rejection could not be excluded.

The children with thrombosis were younger ($P < .04$, Table 2) and of a lower mean body weight ($P < .03$, Table 2) than the other children. Compared with the group without thrombosis, mean preoperative urine production was twice as high in the thrombosis group ($P = .0100$, Table 2, Fig 1). Children with a relatively high diuresis (≥ 36 mL/kg) and thrombosis did not differ from children having the same diuresis but no thrombosis regarding their weight and age of their donor. There was no correlation between age or weight of the recipient and diuresis per

From the Departments of Pediatrics, Medicine, and Surgery, St Radboud University Hospital, Nijmegen, The Netherlands.

Address reprint requests to A.F. van Lieburg, Department of Pediatrics, St Radboud University Hospital, Nijmegen, The Netherlands.

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Table 1. Etiological Factors in Renal Transplant Thrombosis

Young recipients (and low body weight)
High urine production of the native kidneys
Prior native nephrectomy
Primary renal disease
Rejection
Young donors
Status of the donor (PMD or LRD)
Multiple donor vessels
Long cold storage time
Surgical technique
Peroperative hypotension
Cyclosporine immunosuppression
History of multiple fistula thromboses
Renal graft artery stenosis
Use of erythropoietin

Data from references 1 through 20.

kilogram. The number of pretransplant nephrectomies was not significantly different.

With respect to the primary disease, a relatively high incidence of thrombosis was seen in children with a renal hypoplasia or dysplasia ($P < .002$, Table 2, Fig 2). Compared with children with other diseases, age of recipient and donor were not significantly lower in this group.

In the thrombosis group, 2 children received a kidney from a parent. Because in both patients anatomical variations of donor and/or recipient vessels could have attributed to the individual risk of thrombosis, their medical histories are described in detail in the following section.

Table 2. Clinical Characteristics and Surgical Parameters in Transplantations With and Without Thrombosis

	Thrombosis	No Thrombosis	*P* Value
Number of transplants	12	88	
Bilateral nephrectomy in the past (%)	16.7	12.5	NS
Renal hypoplasia/dysplasia (%)	50.0	10.2	<.002
Age of recipient (yr)	7.9 ± 4.0	10.6 ± 3.9	<.040
Body weight of recipient (kg)	21.3 ± 3.1	29.8 ± 12.3	<.030
Preoperative diuresis (mL/kg/24 h)*	40.0 ± 23.8	20.2 ± 20.2	.010
Age of PMD (yr)†	7.2 ± 8.1	18.1 ± 15.1	<.020
Cold storage time (h)	23.5 ± 12.3	28.6 ± 10.0	NS
Anastomosis construction time (min)	39.1 ± 5.3	36.6 ± 9.6	NS
Multiple arteries (%)	16.7	3.4	NS
Multiple veins (%)	8.3	6.8	NS
Treatment with mannitol (%)	66.7	75.0	NS
Treatment with cyclosporine (%)	66.7	60.2	NS
Treatment with erythropoietin (%)	8.3	8.0	NS

*Number of transplants, 12 in thrombosis and 87 in nonthrombosis group.

†Number of transplants, 10 in thrombosis and 83 in nonthrombosis group.

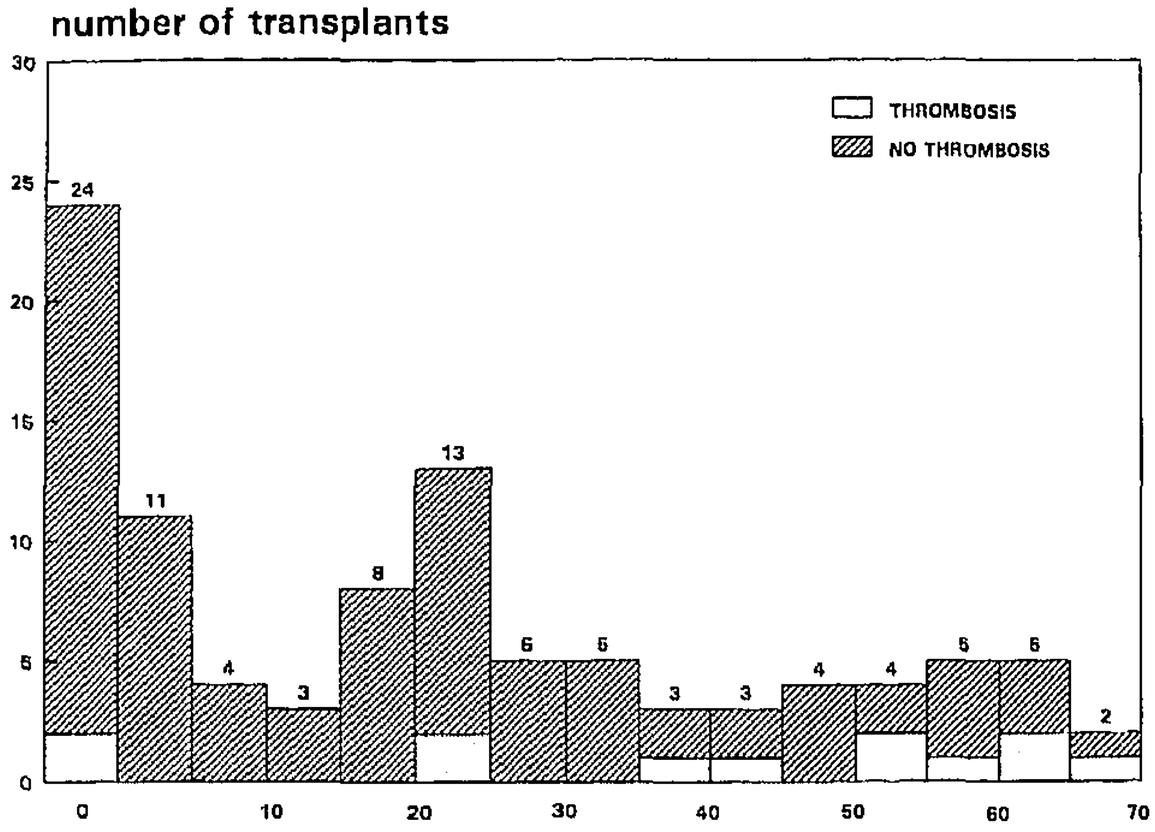

Fig 1. Preoperative diuresis (n = 99 because of lack of quantitative data of 1 incontinent child).

Patient No. 67

The primary disease of patient no. 67 was renal hypoplasia. Hemodialysis was started at the age of 7 years. When he was 11 years old, he received a kidney from his father (age 41). Preoperative diuresis was 36 mL/kg per 24 hours. Immunosuppression was achieved with cyclosporine and prednisone. Intravenous fluid and mannitol were administered as described above. Preoperative angiography of the donor kidney had shown the existence of a small artery supplying the inferior segment of the kidney. This artery was anastomosed end-to-side to the main donor artery. The renal vein was anastomosed to the left vena iliaca externa, that ended in a venous convolute. An extra problem was the minimal length of the donor vein, which made it necessary to implant the kidney upside down. The reconstructed arteria renalis was anastomosed with the arteria iliaca externa. After release of circulation the color of the

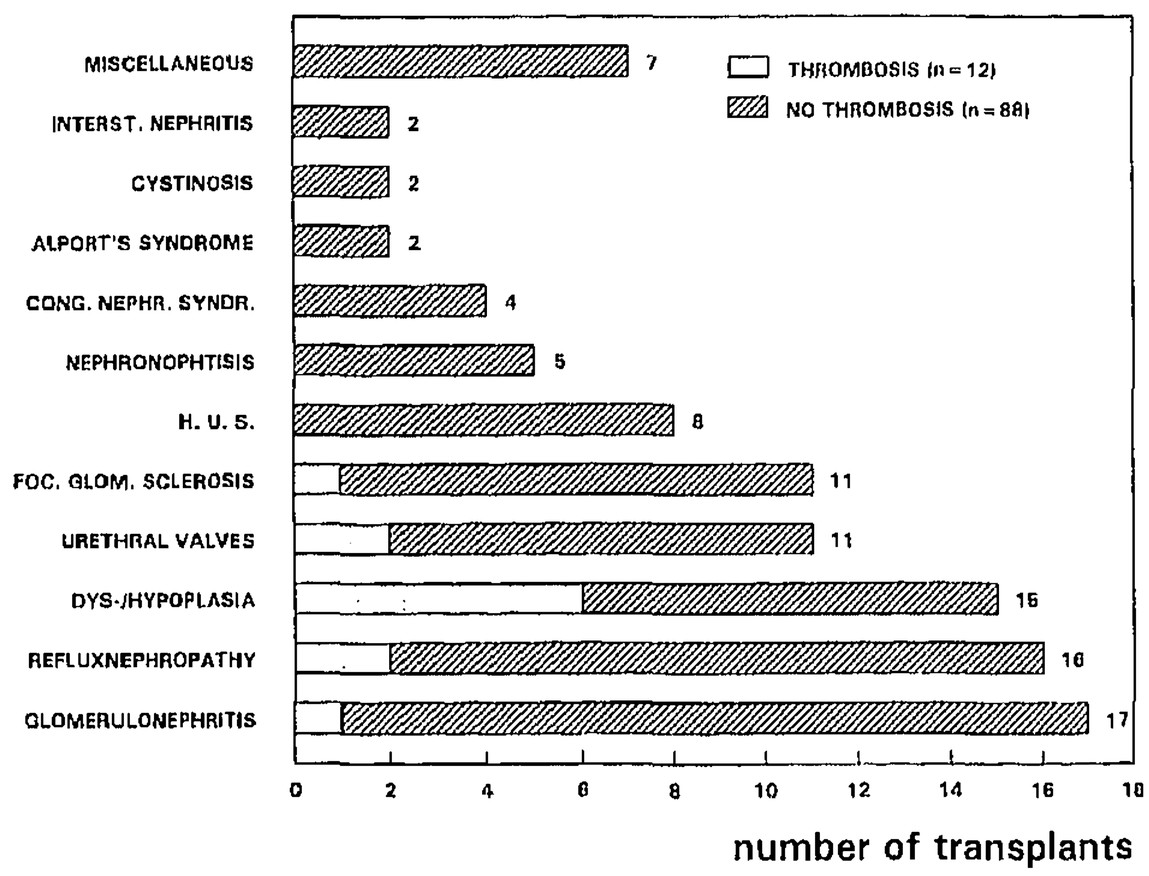

Fig 2. Primary renal diseases.

kidney was adequate and some drops of urine were produced. However, nearly no urine was produced postoperatively. A radionuclide scan was made the same day, which showed no perfusion. At laparatomy it was found that both the renal artery and vein contained a thrombus, and a transplantectomy was performed. Histological examination showed no signs of rejection and was compatible with arterial obstruction.

Patient No. 100

Patient no. 100 was known since birth to have urethral valves and renal failure of moderate severity. At the age of 3 years, continuous ambulatory peritoneal dialysis (CAPD) was started. Because of severe hypertension both kidneys had been removed. When he was 5 years old he received a kidney from his mother (age 32). Immunosuppression was achieved with cyclosporine and prednisone. In addition to the standard fluid management described above, he received albumin because his weight was less than 18 kg and he was the first patient who received low molecular weight heparine (2 dosages of 50 U/kg per 24 hours).

The donor kidney had two veins of different caliber at one patch. The largest vein was anastomosed end-to-side to the vena iliaca communis, the little one was ligated because it was not possible to anastomose it to the main vein. The renal artery was anastomosed to the arteria iliaca communis. After release of circulation the color of the kidney was not immediately adequate and it took about 10 minutes before the first drops of urine were produced. Postoperatively there was nearly no urine production. The same day peritoneal dialysis was necessary because of a high serum potassium level. The next morning a radionuclide scan showed multiple defects. Relaparotomy was performed, and some thrombi were removed from the renal vein. However, this procedure did not result in production of urine. The next day a second scan was made that showed no perfusion, and the transplant was removed. Histological examination showed an obstructing thrombus of the renal vein that seemed to have existed for several days. No signs of rejection were found.

The other 10 children who suffered from thrombosis were grafted with a PMD kidney. Their donors were of a lower mean age than the PMDs in the nonthrombosis group ($P < .02$, Table 2). One of these patients received a kidney with two arteries (no vascular reconstruction). In the total thrombosis group, a predisposition for the occurrence of thrombosis in the presence of multiple arteries or veins could not be shown (Table 2). The time necessary for construction of the anastomosis did not differ significantly from that of the nonthrombosis group, nor did the cold storage time. In one patient diffuse bleeding in the transplant kidney region was detected 1 day before diagnosis of thrombosis. This was the only patient in which hypotension occurred shortly before developing thrombosis. Over the years there has been no essential change in surgical technique or team (two different surgeons were involved), nor was there a clustering of the cases of thrombosis in time. No relation to the use of cyclosporine or its dosage could be detected (Table 2). Thrombosis did not occur in the children with a known renal artery stenosis of the graft (8%). Of the children who suffered from thrombosis, only one had been treated with erythropoietin before transplantation (Table 2). Two others had a history of multiple arteriovenous fistula thromboses. No one was known to have a coagulation disorder.

All thromboses resulted in transplantectomy, mostly within 6 days postoperatively. Only one attempt at thrombectomy was made (see patient no. 100) that failed. All patients who suffered from thrombosis are alive 1 to 10 years after transplantation, 7 of them after a successful retransplantation.

DISCUSSION

Renal transplant thrombosis was reported by Harmon et al[1] with an incidence of 2.6% in 1,045 transplantations in children. Recent figures of this multicenter study after performing 1,667 transplantations show an incidence of 3.4%.[2] LRD recipients younger than 6 years and PMD recipients who received grafts from young donors, especially with a long cold storage time, were found to be at increased risk for thrombosis. Furthermore the risk in LRD recipients in the youngest age group turned out to be significantly larger if no prior dialysis had taken place. Harmon et al suggested that these children were likely to have a high urine production of the native kidneys and that this could be responsible for the increased risk of thrombosis in the LRD group. They assumed that high diuresis might induce intravascular volume depletion more readily and result in a reduced perfusion of the (larger) donor kidney.[1] When this is true one would expect that pretransplant nephrectomy might lower the risk of thrombosis.[3] However, Harmon et al could not confirm this. Recently, Sheldon et al[5] put even more emphasis on the influence of low flow states, but did not base this influence on facts. The present study quantifies the relation between high urine output of the native kidneys and thrombosis. No difference in the number of pretransplant nephrectomies was found, but this could be because this operation is not performed very

often in our center. The observation that children with renal hypoplasia or dysplasia, who are generally polyuric, developed thrombosis more often, draws the attention toward the influence of the primary renal disease. Harmon et al[1] did not detect this relationship, possibly because of the grouping of hypoplasia in one category with aplasia. The predisposition for thrombosis was less obvious in children with urethral valves, who generally have dysplastic kidneys too, but the relatively high incidence (2 out of 11 children) cannot be neglected.

The most accepted causal mechanism regarding low donor and recipient age seems to be the size of structures. Especially size discrepancy results in technical problems,[4] however, in our thrombosis group all PMDs were children. The presence of multiple vessels makes the procedure more complicated as well, although in this study no relation with the occurrence of thrombosis was found (Table 2). Nevertheless, the relatively high incidence of thrombosis in patients that received a kidney from a LRD could be caused by the presence of variations of vascular anatomy in the two LRD recipients with this complication.

No thrombogenic effect could be ascribed to cyclosporine, although the absence of a decreasing tendency with time regarding the number of thromboses, in spite of an increase of experience, gives food for thought. Several reports on this effect of cyclosporine have been published.[12-19] A defective release of plasminogen activator and high plasma levels of plasminogen activator inhibitor have been found in patients on cyclosporine.[18] Other studies suggest that this could be mediated by a prostacycline deficiency.[19]

The small number of patients (n = 8) treated with erythropoietin does not allow us to exclude the possibility that this treatment increases the risk of thrombosis, although no significant difference was found (Table 2).

The observation that in the present study 80% of graft failures in the first 60 days after transplantation were caused by thrombosis once more emphasizes the importance of prevention of this problem. Because high urine production turned out to be a risk factor in our center, we reconsidered our fluid management. In our opinion the amount of saline/glucose and mannitol solution administered is sufficient to correct for insensible water loss and third spacing. In the past, when dialysis was necessary just before transplantation, our goal was to achieve normal dry body weight. However, since 1989, we leave some overhydration. Davidson et al[21] stated that high-dose albumin infusion (1.2 to 1.6 g/kg) is associated with a significant decrease of nonfunction rates. Furthermore favorable results of prophylactic administration of low molecular weight heparin in patients with a predisposition for thrombosis have been reported.[11] These findings made us decide to change our policy; we introduced albumin in higher dosages (1 g per kilogram of body weight) during operation in all patients. Moreover, we now administer low molecular weight heparin if recipients weigh less than 20 kg or if donors are younger than 6 years.

It is concluded that, in addition to young age of the recipient and donor and low weight of the recipient, high preoperative diuresis deserves attention when assessing the individual risk for thrombosis. In a prospective study we will evaluate the effect of addition of heparin and larger amounts of albumin to our perioperative regime.

ADDENDUM

After the series of 100 transplantations described above, 40 additional pediatric transplantations were performed in our hospital, two of which were complicated by thrombosis (4.8%).

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