Low dose aspirin as prophylaxis against renal-vein thrombosis in renal-transplant recipients

Amanda J. Robertson, Vinod Nargund, Derek W. R. Gray and Peter J. Morris

Nuffield Department of Surgery, Oxford Transplant Centre, Churchill Hospital, Headington, Oxford, UK

Abstract

**Background.** Renal-vein thrombosis (RVT) is an infrequent event that accounts for a high proportion of early renal allograft losses, since graft failure secondary to acute irreversible rejection is now relatively rare. The cause of RVT may be related to technical problems, clotting disorders, diabetes, or cyclosporin, but is often difficult to define.

**Methods.** This retrospective study was performed to examine the influence of aspirin on the incidence of RVT in cadaveric and living-related renal transplant recipients receiving cyclosporin-based triple immunosuppression. The Oxford Transplant Centre database was used to identify all early (<30 day) non-immunological graft failures and case histories were examined for clinical and pathological evidence of RVT. In July 1991, aspirin (75 mg o.d. starting immediately before and continuing for 1 month post-transplant) was introduced as routine prophylaxis against RVT. Prior to this, aspirin prophylaxis was not used.

**Results.** In the 6-year period from July 1985 to June 1991, there were 27 cases of RVT in 475 transplants (5.6%). In the subsequent 6-year period, there were six cases of RVT in 480 transplants (1.2%) (P < 0.01).

**Conclusion.** Although not abolished, this indicates a significant reduction in the incidence of RVT with the addition of low-dose aspirin.

**Keywords:** low-dose aspirin; prophylaxis; renal-transplant recipients; renal-vein thrombosis; retrospective study

Introduction

Renal-vein thrombosis (RVT) is a rare complication of renal transplantation but a common cause of early graft loss. It is reported to occur with an incidence of between 0.4% [1] and 6% [2] of all renal allografts. Sometimes a cause can be identified, such as a technical problem with the vein, or extension of a lower-limb venous thrombosis. Other associated factors include cyclosporin, diabetes, high haematocrit, and factor V Leiden mutation, but commonly no aetiopathological factor can be identified. RVT usually results in loss of the graft because of delay in diagnosis and infarction of the kidney. Occasionally, RVT can be life-threatening with graft rupture and haemorrhage. From July 1991, aspirin was introduced in our unit for 1 month post-transplant in an attempt to reduce the incidence of RVT.

Subjects and methods

The Oxford Transplant Centre Database was examined to identify all early (<30 day) non-immunological graft failures. The patient records of all cases where the diagnosis was not listed, was ambiguous, or was recorded as RVT, were examined for clinical and pathological evidence of RVT. Complete information was obtained for 66 records; there were no missing records. Information was retrieved from the patients' notes, including operative details from the hand-written and typed reports and pathology reports, the 'flow chart' that follows the clinical course of the transplant, the computerized record system 'Proton' and the prospective unit database. RVT can rarely occur as a late event but this study was confined to cases of early RVT, as the pathology is probably different. This included some cases where rejection of varying severity was present at some time prior to eventual graft loss, but thrombosis was a significant independent feature. However, grafts that had been rejected where immunosuppression was abandoned, then a later nephrectomy was found to have thrombus present in the renal vasculature, were excluded provided there was no evidence to support thrombosis being a significant contributor to the failure of the graft. Cases of primary renal artery thrombosis were not included.

For comparison, two 6-year periods were chosen, from July 1985 to June 1991 and from July 1991 to June 1997. Living related and cadaveric transplants and first and subsequent transplants were included in the study, giving a total of 955 transplants. Cyclosporin-based immunosuppression was given throughout this time as triple therapy, using cyclosporin (10 mg/kg/day), azathioprine (1.5 mg/kg/day), and prednisolone (20 mg/day for patients >60 kg, 15 mg/day for patients <60 kg, decreasing after 2 months, to 5 mg/day by the end of the first year). Forty-eight patients were given mycophenolate in place of azathioprine within trial protocols.

**Correspondence and offprint requests to:** Mr D. W. R. Gray, Oxford Transplant Centre, Churchill Hospital, Oxford OX3 7LJ, UK.

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from October 1992 to September 1994. In July 1991, aspirin was introduced as prophylaxis for all patients undergoing renal transplantation in an attempt to reduce the incidence of RVT. The standard dose was 75 mg once daily for 1 month post-transplant. Patients who were considered ‘high risk’ because of a history of thrombosis, diabetes, peripheral vascular disease, or other vascular disease were continued on aspirin long-term. Patients with previous renal artery or vein thrombosis were given 150 mg of aspirin per day and continued on aspirin long-term. Ranitidine was given to all patients for 6 months post-transplant for gastric protection against high-dose steroids, but this probably also minimized the risk of gastric irritation from aspirin.

Nuclear renogram was used as the mode of imaging of graft perfusion in most early cases of RVT. Colour duplex Doppler ultrasound has been used as the preferred investigation since 1994. Renal core biopsy and fine-needle aspiration cytology was also utilized to confirm the diagnosis of graft infarction, but in some cases the diagnosis was only apparent at operation. All graft nephrectomy specimens were subjected to pathological examination. Evidence of thrombus in the renal vein at operation and on histological examination has been used for inclusion in this study.

The cases of RVT could be subdivided into primary events, where the kidney was functioning and suddenly underwent thrombosis with no apparent cause, and secondary events, where there was identifiable underlying pathology. Those cases where severe acute rejection was the major histological diagnosis were excluded, even though some evidence of RVT may have also been present, as these were almost certainly primary immunological graft losses.

### Statistics

Statistical significance was calculated using the $\chi^2$ test with Yates correction; significance being taken as $P<0.01$.

### Results

#### Incidence of RVT (Figure 1)

In the 6-year period, from July 1985 to June 1991 there were 27 cases of RVT in 475 renal transplants, giving an incidence of 5.6%. In the 6-year period (July 1991 to June 1997) following the introduction of aspirin, there were six cases of RVT in 480 transplants, giving an incidence of 1.6% ($P<0.01$). Thirty-three episodes of RVT occurred in 31 patients; two patients developed RVT with their first and second grafts (pre-aspirin).

#### Donor and recipient factors

Thirty-two cases of RVT occurred in cadaveric transplants and one in a living related transplant (a third graft). Five patients were pre-dialysis, but close to end-stage renal failure, at the time of transplantation. The thrombosis occurred at a mean of 6.6 days post-transplant (range 2–16 days). Mean recipient age was 45 years (range 22–68 years), which was the same for non-RVT recipients (45.3 years) and 19 recipients were male. Four patients had episodes of previous thromboses including deep-venous thrombosis (DVT) and pulmonary embolus (PE) (one), retinal-vein occlusion (one), and clotted haemodialysis access (two). Three of these patients were on maintenance oral anticoagulation and this was reversed before transplantation, although aspirin was given to the patient with a past history of DVT and PE (post-1991). Peri-operative heparin was given to eight other patients, all before 1991. Aspirin was given to the six patients who sustained RVT after July 1991, including one patient who also received low-dose heparin.

The underlying causes of renal failure in the patients who developed RVT are shown in Table 1. Only diabetic nephropathy was significantly more common in patients who suffered thrombosis. Known risk factors for thrombosis were present pre-operatively in some patients, detailed in Table 2.

<table>
<thead>
<tr>
<th>Causes</th>
<th>$n$ (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy</td>
<td>8 (26)</td>
<td>$&lt;0.01^*$</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>6 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Calculi</td>
<td>5 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>4 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Adult polycystic kidney disease</td>
<td>2 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Varied other causes</td>
<td>6 (19)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not statistically significant vs patients without thrombosis; *vs 8% diabetes in patients without thrombosis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple arteries</td>
<td>30%</td>
</tr>
<tr>
<td>Multiple veins</td>
<td>15%</td>
</tr>
<tr>
<td>Paediatric kidney (&lt;18 years)</td>
<td>15%</td>
</tr>
<tr>
<td>Cold ischaemia time</td>
<td>1527 min</td>
</tr>
<tr>
<td>Cross-match not negative</td>
<td>NS**</td>
</tr>
<tr>
<td>Hb 9.5 g/l</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet count 245×10^9/l</td>
<td>NS</td>
</tr>
<tr>
<td>Primary non-function rate (vs 20%)</td>
<td>50%</td>
</tr>
</tbody>
</table>

NS, not statistically significant vs patients without thrombosis. ** incomplete data; *** mean values.

![Fig. 1. Time plot to show kidney-graft renal-vein thromboses from July 1985 to June 1997. The period since the introduction of aspirin is indicated by shading.](image-url)
Clinical features

Some patients with RVT had concurrent thromboses of other sites as detailed in Table 3. Nineteen cases presented as primary RVT with no other pathology present, either clinically or on histological examination. Secondary RVT included five cases with histological acute rejection, which may have been a contributory cause of RVT and graft loss. Four patients sustained peri-operative cardiac arrest, and despite resuscitation the kidney thrombosed and infarcted, almost certainly secondary to hyperperfusion of the graft. In addition, two patients sustained periods of hypotension which resulted in RVT. Technical problems with the renal vein accounted for two cases and in another case a clotting disorder was suspected.

Fine-needle aspiration cytology was performed on 11 transplants with deterioration in graft function, and this demonstrated necrotic kidney cells. Twelve ‘Tru-cut’ needle core biopsies were obtained from grafts with poor graft function; nine demonstrated renal infarction or necrosis, two were normal and one showed signs of rejection. All subsequently underwent graft nephrectomy for RVT. Twenty-nine grafts were pale and infarcted at the time of exploration. Three kidneys were found to be grossly swollen with capsular splits and surrounding haematoma. In one case, thrombectomy of the renal vein was attempted, but nephrectomy of the infarcted kidney was performed the following day. Thrombectomy of the external iliac vein was performed as required.

Discussion

RVT is a rare complication of renal transplantation but a common cause of early graft loss, occurring with a reported incidence between 0.4% [1] and 6% [2]. The majority of RVT cases occur between 3 and 9 days after transplantation [3] and in our series the mean time was 6.6 days. Commonly, no cause can be found, although certain conditions have been associated with RVT. The main preventable factors are technical problem with the transplant renal vein such as damage to the vein at the time of retrieval, repair of the vein, or twisting of the vein at implantation or on positioning of the kidney [4]. Small veins such as those in paediatric kidneys or kidneys with multiple veins may also predispose to thrombosis. Occasionally RVT is a consequence of extension of a lower limb venous thrombosis or external iliac vein thrombosis which occludes the venous outflow of the graft and results in thrombosis.

Following the introduction of cyclosporin, RVT was felt to be more common with an incidence in one Unit of 7.6% in patients taking cyclosporin, compared with 1.1% in patients on azathioprine and steroid [5]. Our own experience also suggested an increased incidence of thrombosis since the introduction of cyclosporin [2]. Cyclosporin reduces renal blood flow [6], causes increased levels of thromboxane [7], and reduces the production of prostacyclin by endothelial cells [8]. In addition, high levels of cyclosporin may cause endothelial cell damage [9] and can enhance platelet aggregation [10], all potentially predisposing to RVT. Transplant patients taking cyclosporin have been shown to be hypercoagulable, compared to other surgical patients in the early post-operative period [11].

In the 499 transplants at our centre prior to the introduction of cyclosporin, there were only six cases of RVT (1.2%). Graft vessel thrombosis has been reported with the use of OKT3 [12], but there are no reported cases with tacrolimus or mycophenolate. One of our patients on mycophenolate 3 g/day (in addition to cyclosporin and prednisolone) suffered RVT on aspirin, although post-operative cardiac arrest was the more likely underlying cause.

Another risk factor for RVT includes transplantation into a diabetic recipient [13] and our findings agree with this (Table 1). Activated protein C resistance is strongly associated with the risk of venous thrombosis [3] and in our series the mean transplant time was...
long-term. It was felt that the majority of RVT cases were related to platelet dysfunction and although there was no evidence to support the choice of low-dose aspirin, it was felt to have sufficient anti-platelet activity to be effective. The major defect caused by cyclosporin is of platelet function with enhanced platelet aggregation [10], hence the need for an antiplatelet agent such as aspirin. Anticoagulation with heparin or warfarin was not thought to be protective against RVT; indeed thrombosis has occurred with full heparinization [4]. An obvious concern must be the risk of bleeding in patients undergoing transplantation with a vascular anastomosis, and biopsies after transplantation. Unfortunately collection of prospective mortality and morbidity data was only begun in 1991. The data is shown in Table 4. It is difficult to be sure of the role of aspirin in these cases as we do not have complete morbidity data before 1991, although it is likely to be at least a contributing factor. Clinically relevant bleeding following transplant biopsy has been reported to occur between 0.3 and 12.6% [18,19]. Fortunately, gastrointestinal bleeding has not been a problem in our unit, probably because the majority of patients only receive aspirin for 1 month and also receive peptic ulcer prophylaxis.

In conclusion, routine use of low-dose aspirin has been shown in this retrospective study to result in a statistically significant reduction in the risk of RVT in renal transplant recipients receiving cyclosporin-based immunosuppression. This study is not a prospective randomized trial; indeed it is unlikely that such a trial would be undertaken as RVT occurs with such a low incidence. It would require the participation of many centres with similar protocols to get adequate numbers, and a treatment arm without aspirin may be difficult to justify, given the results of our study. Despite the theoretical deficiencies, this study was performed over a period when the immunosuppression protocol was kept remarkably stable (cyclosporin-based triple therapy), and data retrieval was thorough, with 100% follow up and histological confirmation of the cause of graft loss in every case. We are aware of at least six other major transplant centres that use aspirin prophylaxis following renal transplantation in a manner similar to that described here. At the time of writing, this study represents the best evidence (indeed the only evidence so far), that this common practice is effective.

References


Table 4. Bleeding complications (data only since 1991) (13 cases of major bleeding following the introduction of aspirin (2.7%))

<table>
<thead>
<tr>
<th>Cause</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-biopsy</td>
<td>8 (1.6% of biopsies)*</td>
</tr>
<tr>
<td>Early post-transplant</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Re-exploration for bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Graft loss directly attributable</td>
<td>0</td>
</tr>
</tbody>
</table>

*Previous reports 0.3–12.6%.