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Low molecular weight heparin prophylaxis increases the incidence of lymphocele after kidney transplantation[1)]

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ABSTRACT

Lymphocele formation after kidney transplantation has become more frequent at our department after the introduction of routine thromboembolic prophylaxis with low molecular weight heparin (LMWH). A consecutive series of 130 kidney transplant recipients were included in a retrospective study. Fifty-eight patients received prophylaxis and 72 did not. Other background data between the two patient groups was comparable. Lymphocele was diagnosed by ultrasound. Lymphocele formation was significantly more common ($p<0.01$) among patients who received LMWH prophylaxis (43%) than patients who did not (20%). There was no increase in bleeding-related complications in the prophylaxis group. An interesting finding was that, in the prophylaxis group, fewer grafts were lost due to vascular complications or early rejection, leading us to conclude that the use of LMWH increases the incidence of lymphocele formation after kidney transplantation, but may also reduce early graft loss due to thrombosis and vascular rejection.

Key words; Kidney transplantation, heparin prophylaxis, lymphocele, graft loss

INTRODUCTION

Lymphocele formation is a well-known complication after kidney transplantation. Lymphoceles can obstruct the ureter, compress the kidney or its vessels, and cause graft dysfunction or even graft loss. Several risk factors for developing lymphocele have been discussed in related literature. Lymphocele has been attributed to high doses of steroids (1,2), rejection episodes (1,2), tubular necrosis (1), diuretics (2), retransplantation (3), and anticoagulation therapy (2).

After introduction of routine prophylactic treatment with low molecular weight heparin (LMWH) at our clinic, we noticed an increased incidence of lymphocele for-

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mation. We have therefore investigated, in a retrospective study, whether the use of LMWH may be added to the risk factors for lymphocele formation after kidney transplantation.

MATERIAL AND METHODS

A consecutive series of 130 kidney transplant recipients were included in the retrospective study. Patients' charts were used to collect data on demographics, underlying diagnosis, coagulopathies and preoperative anticoagulant therapy.

Lymphocele was defined as a perirenal fluid collection identified by ultrasonography, where urinary leakage and haematoma could be ruled out. The ultrasound was performed by radiologists with extensive experience in examination of kidney transplant patients. Urinary leakage was diagnosed by measurement of creatinine in the fluid collection or drainage.

Of the 130 transplant patients, 58 received LMWH prophylaxis and 72 did not. Two patients in the prophylaxis group and 8 in the non-prophylaxis group did not undergo postoperative ultrasonographic examination and were therefore not included in further analysis. None of these 10 patients had postoperative complications or rejection episodes. The remaining 120 patients were divided into two groups. Group A with thromboembolic prophylaxis (n=56) and Group B without prophylaxis (n=64). The patient characteristics are summarised in Table 1. In Group A, 53 patients received enoxaparin (KlexaneR, Rhône-Poulenc Rorer) as prophylaxis. Of these 53 patients, 50 received a dose of 20 mg x 1 s. c., and 3 patients received 40 mg x 1 s. c. Of the remaining three patients in this group, one received dalteparinum (FragminR, Pharmacia Upjohn) 2500 IU x 1 s. c., and two received heparin (Heparin, Lövens) 5000 IU x 1 s. c.. The mean duration of prophylactic treatment was 10.4 days (range 0-47). Prophylaxis was initiated per- or perioperatively.

All patients were operated on by the same surgeons with the same surgical technique. The artery was anastomosed end-to-side to the external iliac artery and the vein end-to-side to the external iliac vein. Careful dissection and ligation of native periiliac lymphatic vessels was performed in all patients.

The basal immunosuppressive protocol consisted of cyclosporine and steroids.

The two groups were comparable with respect to demographics, underlying kidney disease and type of transplantation (see Table 1). Some patients had a history of thromboembolic complications, and 12 patients in Group A and 3 in Group B were treated preoperatively with acetylsalicylic acid (ASA). This difference was significant ($p< 0.01$). Three patients in Group A were treated also with warfarin: one with cardiac valvular prosthesis, and two with a predisposition for thrombosis. All three received warfarin parallel to thrombosis prophylaxis.

One patient in Group A and four in Group B showed preoperative thrombocytopenia. This difference was not statistically significant.

Table 1. Patient characteristics

	Group A	**Group B**
N	56	64
Age	48 (12–69)	45 (12–72)
Sex male/female	36/20	43/21
Necro/Living donor	41/15	47/17
Retransplantation same side	2	2
Pre-op creatinine (µmol/l)	703 (320–1162)	742 (379–1175)
Platelets<150	1	4
ASA preoperative	12	3
Warfarin preoperative	3	0
Diagnosis:		
Adult polycystic kidney disease	6	12
Glomerulonephritis	17	14
IgA-nephritis (Berger)	6	7
Focal and segmental sclerosis	1	4
Diabetic nephropathy	13	15
Amyloidosis	1	2
Pyelonephritis	1	4
Hereditary nephritis	1	1
Interstitial nephritis	4	1
Other	6	4

STATISTICAL ANALYSIS

Statistical testing for differences in frequencies was performed with c2 analysis and differences in means with analysis of variance (ANOVA).

RESULTS

The results are summarised in Table 2. Lymphocele was found in 37 (31%) patients. Of these, 24 (65%) were treated with prophylaxis (Group A), and 13 (35%) were not (Group B). This difference was statistically significant ($p<0.01$). A total of 7 patients treated preoperatively with ASA developed lymphocele (6 in Group A and one in Group B). ASA in itself, however, did not constitute an independent risk factor ($p=0.16$). None of the patients treated preoperatively with warfarin developed lymphoceles.

Lymphocele was seen in two patients with acute tubular necrosis, both of whom were in the group with prophylaxis.

Twenty-one patients, 10 in Group A and 11 in Group B, underwent treatment of their lymphocele. The treatment was either diagnostic/therapeutic needle aspiration or percutaneous drainage. None of the patients required surgery for their lymphocele.

Table 2. Outcome for the two patient groups

	Group A	Group B
Patients with lymphocele	24	13
Lymphocele requiring treatment	10	11
Time until diagnosis of lymphocele (days)	21 (3-48)	33 (9-125)
In-hospital care (days)	25.9 (median 21)	26.6 (median 22)

Ten patients in the prophylaxis group and 12 patients in the non-prophylaxis group underwent reoperation (see Table 3). Two of these 12 patients in the non-prophylaxis group underwent two reoperations. In 7 reoperated patients, 3 of whom also had lymphocele, reoperation was due to urinary leakage. The number and causes for reoperation were similar in the two groups. One interesting finding, however, was that early transplantectomy was performed only in the non-treatment group, 4 vs. 0. While this difference was not statistically significant (p=0.06), it does show a clear tendency. For three patients, the cause of transplantectomy was early severe rejection, the fourth had a venous thrombosis.

Prophylaxis was not associated with a higher incidence of urinary leakage, bleeding complications, longer postoperative drainage, or lymphocele requiring treatment.

Table 3. Cause of reoperation

	Group A	Group B
Bleeding	4	3
Urine leakage	2	5
Transplantectomy	0	4
Other	4	2

DISCUSSION

The frequency of lymphocele formation after kidney transplantation reported in available literature in the field varies between 5-49%. This can be related to different ways of defining a lymphocele (1, 4-6). Ultrasound has become a routine procedure after kidney transplantation. It is therefore likely that a higher frequency of lymphocele is reported in more recent publications than in earlier reports. In our study, we found lymphocele in 31% of the cases. This is fairly high, but comparable to other investigations where ultrasound has been performed routinely (1,4).

To the best of our knowledge, prophylactic treatment with LMWH has not been reported to be a risk factor for development of lymphocele after kidney transplantation. Braun (2), however, mentions that anticoagulation could be a possible risk factor for lymphocele. In his study, 5 out of 15 (33%) patients who received anticoagu-

lation therapy in connection with transplantation developed lymphocele. In other types of surgery, especially after extraperitoneal pelvic lymphadenectomy, postoperative lymphocele and increased postoperative drainage fluid have been associated with thromboembolic prophylaxis. In these studies, the patients were treated with Heparin and not LMWH (7-9).

There are two main causes for the development of lymphocele after kidney transplantation: leakage from lymph vessels along the iliac vasculature, and leakage from the kidney, especially when it has been decapsulated (10).

We see two possible mechanisms that can explain the role of anticoagulation as a risk factor for the development of lymphocele formation. One is that anticoagulation therapy influences the ability of blood to clot, thereby impairing the sealing of lymph vessels in the wound. This impairment is added to the defective homeostasis associated with uraemia, which is verified by prolonged bleeding time (11). Secondly, lymph, like plasma, contains coagulation factors (12). Its clotting ability can therefore be affected by anticoagulation therapy.

Our observation that LMWH increases the incidence of lymphocele forced us to reconsider and to weigh the pros and cons on giving routine LMWH prophylaxis to all transplant recipients. Lymphocele formation is clearly a complication that bears a potential hazard for the graft and could necessitate reoperation or other therapeutic measures. However, none of our patients required reoperation due to the lymphocele. The median hospital stay was also similar for the two groups, indicating that there was no major difference in cost or morbidity between the two groups. However, 10 patients in the prophylaxis group and 11 in the non-prophylaxis group required a percutaneous puncture or drainage of the lymphocele. In all cases, this was performed without further complications. The adverse effects of giving LMWH prophylaxis thus seem limited.

What then are the advantages of giving routine LMWH prophylaxis? The main advantage is prevention of thromboembolic complications. In this small series of patients, it is not possible to demonstrate such an effect, but we know from experience that transplant recipients can develop venous thromboembolism and that this risk may be enhanced under cyclosporine treatment (13,14). It is therefore reasonable to assume that prophylaxis in this patient group holds the same benefits as for patients undergoing general surgery.

Another advantage might be the reduction of the risk of early graft thrombosis. None of the patients in the group that received prophylaxis developed graft thrombosis, despite there being significantly more patients in this group with a history of thromboembolic complications and preoperative treatment with ASA or Warfarin. This indicates that prophylaxis may help to prevent graft thrombosis.

Our results also indicate that LMWH may reduce the incidence of graft loss due

to early severe rejection. One explanation for this finding could be that heparin and heparin analogues not only have an anticoagulant effect but also reduce the inflammatory reaction and damage to the endothelium (15). Heidenreich et al.(16) also report a high rate of acute rejections in renal allograft recipients with thrombophilic risk factors. However, these findings need to be further elucidated in future prospective randomised studies.

We have introduced routine LMWH prophylaxis for all kidney transplant recipients. One could, however, argue that prophylaxis should be given only to patients with increased risk of developing thrombosis, such as recipients with elevated platelet counts (17), extreme donor age, female donors and prolonged ischemia time (18), OKT3 monoclonal antibody treatment (19,20), or kidneys with multiple arteries (21). Patients with none of these associated risk factors can, however, still develop graft thrombosis. With a one-year graft survival of about 85%, graft thrombosis has become one of the major causes for early graft failure (22,23). The incitement for giving prophylaxis has thus become stronger and if, as suggested by our study, LMWH prophylaxis reduces the incidence of early graft loss due to severe rejection, the indication for prophylaxis is further strengthened.

In summary, as it has several potential benefits and the hazards seem to be limited, we advocate that kidney transplant recipients should receive LMWH prophylaxis.

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