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Risk Factors and Management of Venous Thromboembolic Diseases in Donor of Living Donor Liver Transplant

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ABSTRACT

Background: liver transplantation surgically replaces a failing or diseased liver with one that is normal and healthy. At this time, transplantation is the only cure for liver insufficiency or liver failure because no device or machine reliably performs all of the functions of the liver. **Aim of the Work:** this study aimed to highlight risk factors of the venous thromboembolism in donors of living donor liver transplant and its management.

Patients and Methods: this study included 40 patients who underwent hepatectomy for living donor liver transplant. All patients were evaluated extensively, including history and physical examination and specialty consultations when indicated. All patients did haematological studies to detect the risk factors of thromboembolic disease. **Results:** in patients with manifestations of venous thromboembolism 2 donors have single risk factor for venous thromboembolism and 4 donors have double risk factors. **Conclusion:** presence of multiple risk factors for venous thromboembolism led to increase in its incidence, so during preoperative assessment of the donors, if they have multiple risk factors for thrombosis some precautions should be taken to avoid venous thrombosis. **Recommendations:** preoperative precautions include heamatological consultations for the donors and prophylaxis dose of anticoagulant. Intra operative precautions included pneumatic calf pressure, elastic stocking. Finally postoperative precautions should be continued , these donors should take therapeutic doses of anticoagulants and follow up by lower limb venous duplex.

Keywords: venous thromboembolic disease, living donor liver transplant.

INTRODUCTION

Liver transplantation or hepatic transplantation is the replacement of a diseased liver with some or all of a healthy liver from another person (Allograft). The most commonly used technique was phototropic transplantation, in which the native liver was removed and replaced by the donor organ in the same anatomic location as the original liver. Liver transplantation is a viable treatment option for end-stage liver disease and acute liver failure [(1)].

Liver transplantation is now performed at over one hundred centers in the US, as well as numerous centres in Europe and elsewhere. One-year patient survival was 80-85% and outcomes continue to improve, although liver transplantation remains a formidable procedure with frequent complicatio**.**For adult-to-adult living donor liver transplantation, we have preferred the right lobe (Segment V, VI, VII and VIII) [(2)].

Donor evaluation is one of the most important aspects of adult-to-adult living donor liver transplantation. The evaluation process should reveal any conditions that may predispose the healthy donor to any intra and post-operative complications including hemorrhage, bile leakage due to bile track truma or even death. Almost all donors experience short-term liver dysfunction and routine blood count abnormalities [(3)]. Although laboratory test results may guide surgery and identify complications earlier, some complications may lead to physical, mental, and psychosocial problems that affect the quality of life and psychological outcomes of living donors after transplantation. Therefore, it is important to precisely evaluate the surgical complications, liver dysfunction and quality of life of living donors after operation. Initially, the work-up included endoscopic retrograde cholangiography; this has since been replaced by Cholangio MRI [(4)].

One of the complication for living donor liver transplant is venous thromboembolism. the risk factors for venous thromboembolismmay congenital or aquired congenital risk factors included deficiencies or defects in natural anticoagulants, such as antithrombin, protein C and protein S and genetic polymorphisms such as prothrombin G20210A and cleavage-resistant forms of factor V. Acquired risk factors included antiphospholipid antibodies, detected as lupus anticoagulants and/or anticardiolipin antibodies and/or anti-beta-2-glycoprotein-I antibodies. High levels of clotting factors, dysfibrinogenemia, hyperhomocysteinemia, prolonged immobilization, increasing age, surgery, trauma, cancer, obesity, poor nutrition, pregnancy, oral contraceptives and hormone replacement therapy [(5)].

One of the risk for venous thromboembolism was factor v leiden. Factor v leiden is a genetic disorder characterized by a poor anticoagulant response to activated protein c and an increased risk for venous thromboembolism. Deep venous thrombosis and

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pulmonary embolism are the most common manifestations, but thrombosis in unusual locations also occurs. Diagnosis requires the activated protein c resistance assay (A coagulation screening test) or DNA analysis of the F5 gene, which encodes the factor v protein [(6)].

Preoperative evaulation tests for venous thromboembolismincludes protein c and protein s levels, antithrombin III level, lupus anticoagulant, activated protein c resistance (Factor 5 Leiden mutation tested if positive), prothrombin gene mutation (PG202A), antiphospholipid antibodies (anti-cardiolipin antibody and beta 2 glycoprotein antibody) [(7)]. Post operative patient may presented by dysnea, chest pain due to pulmonary embolism and diagnosis by D dimar and CT angiography on pulmonary artery or presented by limd swelling and pain in calf muscle due to deep vein thrombosis and diagnosis by douplex study on veins system of the effected limb [(8)]. Prevention of primary manifestations: In the absence of a history of thrombosis, long-term prophylactic anticoagulation is not routinely recommended for asymptomatic factor V Leiden heterozygotes. A short course of prophylactic anticoagulation when circumstantial risk factors are present may prevent initial thrombosis in factor V Leiden heterozygotes [(9)]. The first acute thrombosis is treated according to standard guidelines (Initial course of intravenous unfractionated heparin or low molecular-weight heparin and initiation of warfarin. The duration of oral anticoagulation therapy is debated. Long-term oral anticoagulation is considered in those with recurrent VTE, multiple thrombophilic disorders, or coexistent circumstantial risk factors and, in factor V Leiden homozygotes [(10)].

The use of thrombolytic agents such as streptokinase, urokinase and recombinant tissue-type plasminogen activator (r-tPA) in the treatment of deep vein thrombosis (DVT) aims to bring about clot lysis (breakdown of the clot) and rapid normalisation of venous blood flow. These agents can be given via 'catheter directed' (referred to as 'catheter or vein directed' in the evidence of this chapter) administration or 'systemic' administration. 'Catheter directed' administration involves the infusion of the drug by a catheter inserted directly into the affected veins whereas 'systemic' administration involves administration of the drug into an unaffected peripheral vein which then allows the drug to be carried in the circulation to the affected veins [(11)].This study aimed to highlight risk factors of the venous thromboembolism in donors of living donor liver transplant and its management.

PATIENTS AND METHODS

Patients

This study included 40 patients underwent hepatectomy for living donor liver transplant. All patients were evaluated extensively, including history and physical examination and specialty consultations when indicated. All patients were done haematological studies to detect the risk factors of thromboembolic disease.

Inclusion criteria

1) Male or female patients
2) Age from 18 to 45years in case of first degree relative donors or from21-45years in case of non-relative donors
3) Medically free(no past medical history).
4) Surgically free (no past history of upper abdomen surgery).
5) Body mass index 18-28.

Exclusion criteria

1) Age more than 45 years old.
2) Medical problems as:
-Hypertension
-Diabetes
-Ischemic heart diseases
-Uncontrolled hyperlipidemia
3) Factor 5 leiden homozygous

METHODS

Perioperative assessment:

Preoperative studies will include:

- Complete blood count, urine analysis, serum chemistries, electrocardiogram, and abdominal ultrasound.
- Blood group and Rh type which should matching with the recipient.
- Liver function tests will be performed including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline Phosphatase, total proteins, albumin and hepatitis markers.
- Lipid panel will be assessed including total cholesterol, serum triglycerides, high density lipoproteins (HDL), and low density lipoproteins (LDL).

Nutritional assessment

- INR, S.ferritin, fasting blood glucous level.
- Urine for drug abuse
- Tumor markers as alpha-feto protein.
- Coagulation profile including factor 5 leiden gene mutation, protein c, protein s ,antithrombin 3 and lupus anti-coagulant.
- MRCP, CT volumetery, CT venography, CT arterigraphy, CTportography and liver biopsy.
- All donors should stop smoking 3 monthes preoperative.

Operative:

Surgical hepatectomy operations for living donors liver transplant will be carried out on 40 patients either :

- Left hepatic lobe graft.

- Right hepatic lobe graft.

Prevention measurements including pneumatic calf pressure, elastic stocking.

Post-operative assessment:

In the postoperative period all patients will be assessed for:

1. Recovery from surgery.
2. Hospital stay.
3. General early postoperative complication (chest complications, wound infection...)
4. Complications of surgery.

Follow-up by:

1. Hepatic dopplexdaily .
2. Full laboratory studies daily.
3. Lower limb venous dopplex 14 days posoperative.
4. CT pulmonary angiography if needed in addition to D-dimar.
5. Prophylaxis dose of clexane (40 mg/24H).

The study was approved by the Ethics Board of Ain Shams University.

RESULTS

Results of our study involved 40 patients who underwent hepatectomy for living donor liver transplant in Ain-Shams Specalized Hospitals. They were selected upon the selection criteria adopted for this study.

Demogeraphic data:

The patients were 9 females and 31 males. Their ages ranged from 18-44 years with mean of age 30.3±6.77. All patients underwent hepatectomy for living donor liver transplant.

Data management and analysis:

Statistical presentation and analysis of the present study was conducted, using the mean, standard Deviation and chi-square test by **SPSS V. 20.**

Mean = $\frac{\Sigma x}{n}$

Where Σ = sum & n = number of observations.

Standard Deviation [SD] :

$$SD = \sqrt{\frac{\Sigma |x - x|^2}{n-1}}$$

Chi-square

The hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Fisher's exact test and Yates' corrected chi-square are computed for 2x2 tables.

Significant level

Non significant >0.05 significant <0.05* - High significant <0.001**

RESULTS

Table 6: number and percent regarding factor 5 Leiden

Factor 5 Leiden	N	%
Normal	37	92.5
Heterozygous	3	7.5
Total	40	100

This table showed number of patents have factor 5 Ledien mutation (Heterozygous genotype)

Table 7: number of patients had venous thromboembolism manifestations

Venous thromboembolism		%
Negative	**38**	95
Positive	**2**	5
Total	**40**	100

This table showed number of patients have venous thromboembolism manifestations (2 patients) one patient complain from deep vein thrombosis and the other have manifestations of pulmonary embolism.

Table 8: number of patients had venous thromboembolism manifestations

Dopplex CT or D Dimar	N	%
Free	33	82.5
CT PA free	1	2.5
DVT	1	2.5
D Dimar	4	10
PE	1	2.5
Total	40	100

This table showed that one patient underwent CT PA but it was free, 4 patients were positive D Dimer, one patient complain from deep vein thrombosis and one show manifestations of pulmonary embolism.

Table 9: showing groups of patients

Groups	N	%
Group I	7	17.5
Group II	33	82.5
Total	40	100

Group 1 showed manifestations of venous thromboembolism

Group 2: showing normal individual

Table 10:showing group 1: 2 donors that had single risk factor for venous thromboembolism and 4 donors had double risk factors

Risk factor	N	%
Non	1	14.29
Single	2	28.57
Multi	4	57.14
Total	7	100.0

Table 11: showing abnormality in risk factors for VTE

	Normal		Abnormal	
	N	**%**	**N**	**%**
BMI	40	100	0	0
Cholesterol	38	95	2	5
T.G	38	95	2	5
HDL	37	92.5	3	7.5
LDL	40	100	0	0
Lupus anticoagul	35	87.5	5	12.5
protein C	38	95	2	5
protein S	40	100	0	0
Antithrombin3	37	92.5	3	7.5
A.S.T	39	97.5	1	2.5
A.L.T	39	97.5	1	2.5
anticardiolibin IgM	38	95	2	5
anticardiolibin IgG	39	97.5	1	2.5

This table showed that:
2 patients have elevated cholesterol level
2 have high T.G level
3 have high HDL level
2 have high protein c level
5 have high lupus anticoagulant level
3 have high antithrombin 3 level
1 has elevated liver enzyme

Table 12: comparison between two groups as regard factor 5 Leiden

Factor 5 Leiden		**Groups**					
		Group I		**Group II**		**Total**	
		N	**%**	**N**	**%**	**N**	**%**
No		5	71.4	32	97.0	37	92.5
Heterozygo		2	28.6	1	3.0	3	7.5
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	5.430					
	P-value	0.020*					

This table showed comparison between no mutation and mutation of factor 5 Leiden (heterozygous genotype) in relation to presence of venous thromboembolism (Group 1) or not (Group 2) with statistical significant deference between two groups as regard Factor 5 Leiden as p-value was <0.05*

Table 13: comparison between the two groups as regard cholesterol

Cholesterol		**Groups**					
		Group I		**Group II**		**Total**	
		N	**%**	**N**	**%**	**N**	**%**
Normal		7	100.0	31	93.9	38	95.0
Abnormal		0	0.0	2	6.1	2	5.0
Total		7	100.0	33	100.0	40	100.
Chi-square	X^2	0.447					
	P-value	0.504					

This table showed comparison between the normal and abnormal cholesterol level in relation to presence of venous thromboembolism (Group 1) or not(Group2).with no statistical significant deference between the two groups as regard cholesterol as p-value was <0.05*

Table 14: comparison between two groups as regard T.G

T.G		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		6	85.7	32	97.0	38	95.0
Abnormal		1	14.3	1	3.0	2	5.0
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	1.540					
	P-value	0.215					

This table showed comparison between the normal and abnormal T.G level in relation to presence of venous thromboembolism (Group 1) or not(Group2)with no statistical significant deference between the two groups as regard T.G as p-value was <0.05*

Table 15: comparison between two groups as regard HDL

HDL		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		6	85.7	31	93.9	37	92.5
Abnormal		1	14.3	2	6.1	3	7.5
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	0.563					
	P-value	0.453					

This table showed comparison between the normal and abnormal HDL level in relation to presence of venous thromboembolism (group 1) or not(group2).with no statistical significant deference between two groups as regard HDL as p-value was <0.05*.

Table 16: comparison between two groups as regard lupus anticoagulant

Lupus anticoagulant		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		3	42.9	32	97.0	35	87.5
Abnormal		4	57.1	1	3.0	5	12.5
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	15.461					
	P-value	<0.001**					

This table showed comparison between the normal and abnormal lupus anticoagulant level in relation to presence of venous thromboembolism (group 1) or not(group2).with highly statistical significant deference between two groups as regard lupus anticoagulant as p-value was <0.001**

Table 17: comparison between two groups as regard protein C

Protein C		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		6	85.7	32	97.0	38	95.0
Abnormal		1	14.3	1	3.0	2	5.0
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	1.540					
	P-value	0.215					

This table showed comparison between the normal and abnormal protein c level in relation to presence of venous thromboembolism (group 1) or not (group 2) with no statistical significant deference between two groups as regard protein C as p-value was <0.05*

Table 18: comparison between two groups as regard antithrombin3

Antithrombin3		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		7	100.0	30	90.9	37	92.5
Abnormal		0	0.0	3	9.1	3	7.5
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	0.688					
	P-value	0.407					

This table showed comparison between the normal and abnormal antithrombin 3 level in relation to presence of venous thromboembolism (Group 1) or not(Group2) with no statistical significant deference between two groups as regard Antithrombin 3 as p-value was <0.05*.

Table 19: comparison between two groups as regard A.S.T

A.S.T		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		7	100.0	32	97.0	39	97.5
Abnormal		0	0.0	1	3.0	1	2.5
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	0.218					
	P-value	0.641					

This table showed comparison between the normal and abnormal AST level in relation to presence of venous thromboembolism (Group 1) or not(Group2).with no statistical significant deference between two groups as regard AST as p-value was <0.05*.

Table 20: comparison between the two groups as regard A.L.T

A.L.T		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		7	100.0	32	97.0	39	97.5
Abnormal		0	0.0	1	3.0	1	2.5
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	0.218					
	P-value	0.641					

This table showed comparison between the normal and abnormal ALT level in relation to presence of venous thromboembolism (Group 1) or not(Group2) with no statistical significant deference between two groups as regard factor 5 Leiden as p-value was <0.05*.

Table 21: comparison between the two groups as regard anticardiolibin IgM

anticardiolibin IgM		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		6	85.7	32	97.0	38	95.0
Abnormal		1	14.3	1	3.0	2	5.0
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	1.540					
	P-value	0.215					

This table showed Comparison between normal and abnormal anticardiolipin IgM level in relation to presence of venous thromboembolism (group 1) or not(group2).with no statistical significant deference between two groups as regard anticardiolipin IgM as p-value was <0.05*

Table 22: comparison between the two groups as regard anticardiolibin IgG

Anticardiolibin IgG		Groups					
		Group I		Group II		Total	
		N	%	N	%	N	%
Normal		7	100.0	32	97.0	39	97.5
Abnormal		0	0.0	1	3.0	1	2.5
Total		7	100.0	33	100.0	40	100.0
Chi-square	X^2	0.218					
	P-value	0.641					

This table showed comparison between the normal and abnormal anticardiolipin IgG level in relation to presence of venous thromboembolism (Group 1) or not(Group2) with no statistical significant deference between two groups as regard anticardiolipin IgG as p-value was <0.05*.

DISCUSSION

Liver transplantation or hepatic transplantation is the replacement of diseased liver with some or all of a healthy liver from another person (Allograft). Indications for liver transplantation can be classified into end-stage liver disease, acute liver failure and certain benign and malignant liver tumors [(12)].

For transplantation we need donors who are healthy people who volunteer to undergo a hepatectomy for living donor liver transplant. This is a unique situation and it is important to assess how they recover after surgery [(13)].

The complications of hepatectomy for liver transplant are divided into the following categories: posthepatectomy liver failure, bile tract injury , abdominal collection, prolonged ileus, gastroparesis, wound complications (wound infection, incisional hernia), deep venous thrombosis (DVT), being cardiovascular (atrial flutter, hypertension, endocarditis), pulmonary (pleural effusion, pneumothorax, bronchopneumonia, pulmonary thromboembolism) and intra-abdominal bleeding) [(14)].

So, one of the complications of hepatectomy for donors is venous thromboembolism (DVT/PE).The rate of DVT/PE after liver transplantation is similar to the rate after other major operations. Patients were more likely to develop DVT/PE if they received increased amounts of intraoperative cryoprecipitate/fresh frozen plasma (FFP) or had an elevated postoperative INR. Furthermore, patients with a complicated postoperative course have the highest risk of venous thromboembolism [(15)].

In this study, we dealt with 40 patients which underwent hepatectomy for living donor liver transplant with inclusion criteria such as: age from 18 to 45years in case of first degree relative donors or from21-45years in case of non-relative donors, medically free (no past medical history), surgically free (no past history of upper abdomen surgery) and body mass index 18-28). Exclusion criteria included: age more than 45 years ,medical problems as: hypertension-diabetes -ischemic heart diseases-uncontrolled hyperlipidemia and factor 5 Leiden homozygous.

In our study, the documented cases showed venous thromboembolism manifestations such as**:**

One patient complain from redness, hotness and swelling in calf muscle. By local examination there was tender tense calf muscle, the patient underwent Dopplex study at the 4th day post operative which show acute popliteal vein thrombosis.

One patient complain from dysnea and severe chest pain, the patient underwent CT on pulmonary artery which gave picture of pulmonary embolism.

In addition to 4 patients had positive D dimar and one patient showed same manifestation of pulmonary embolism, but CT on pulmonary artery was free.

So in our study, the percentage of patient underwent hepatectomy and showed manifestation of venous thromboembolism was 5%, while in other study [(16)] which was a retrospective review of 917 patients over 15 years at a single center post transplantation VTE manfestations occurred up to 1 year after liver transplantation.Among 917 patients, VTE occurred in 42 (4.58%) patients. 12 had PE and 33 had DVT events.

The risk factors for venous thromboembolism may be congenital or acquired. Congenital risk factors included deficiencies or defects in natural anticoagulants, such as antithrombin, protein c and protein s, and genetic polymorphisms such as prothrombin G20210A and cleavage-resistant forms of factor v. Acquired risk factors included antiphospholipid antibodies, detected as lupus anticoagulants and/or anticardiolipin antibodies and/or anti-beta-2-glycoprotein-I antibodies, prolonged immobilization, increasing age, surgery, trauma, cancer, obesity, poor nutrition, pregnancy, oral contraceptives and hormone replacement therapy [(5)].

In our study, 7 patient showed manifestations of venous thromboembolism 2 of them had hyperlipidemia (28.57%), while other in another study which was done by **Bottaro *et al*.** [17] which was a descriptive, retrospective, comparative, cross-sectional study including a group of 313 patients with venous thromboembolism (VTE). All patients were subjected to a lipid profile study with determination of total cholesterol, high density lipoprotein cholesterol (cHDL), low density lipoprotein cholesterol (cLDL) and triglycerides. They found that the percentage of patients having VTE and hyperlipidemia was 31%.

One of the risks for venous thrombo embolism was factor Vleiden. Factor V Leiden is a genetic disorder characterized by a poor anticoagulant response to activated protein c and an increased risk for venous thromboembolism. Deep venous thrombosis and pulmonary embolism are the most common manifestations [6].

In our study, we found that 3 patients showed factor 5 leiden mutation (Heterozygous genotype) one of them suffered from venous thromboembolism manifestation, while 37 patients showed no mutation and one of them had pulmonary embolism, in **Hirshfield *et al.*** [18] study which dealt with 276 donors of liver transplant showed that 19 patients had positive heterozygous state (6 showed venous thromboembolism manifestation and 13 had no manifestation).

In our study, two patient complained from venous thromboembolism one of them had positive heterozygous state, while in **Hirshfield *et al.*** [18] 12 showed manifestation of venous thromboembolism and 6 had positive heterozygous state.

We found that the percentage of patient with positive heterozygous state in our study was7.5%, while they were 6.9% in **Hirshfield *et al*.** [18] study.

The percentage of patient with no mutation was 92.5% in our study, while it was 93.1% in **Hirshfield *et al*.** [18] study

The percentage of patient showed venous thromboembolism manifestation 5% in our study and 4.3% in **Hirshfield *et al*.** [18] study

The percentage of patient showed venous thromboembolism manifestation with heterozygous state 50% in both studies, while percentage of patients showed mutation with no manifestation 5% in our study and 407% in **Hirshfield *et al*.** [18] study

In another study done by **Arsov *et al.*** [19] which was a retrospective case-control study involved 190 patients with venous thromboembolic disease and 200 healthy individuals.The prevalence of factor v Leiden mutation among patients with venous thromboembolic disease was 21.1%, compared to 5.5% in the healthy individuals.

Antiphospholipid antibodies syndrome are a heterogeneous family of immunoglobulins that include, lupus anticoagulants and anticardiolipin antibodies. Thromboembolic events were reported in approximately one third of antiphospholipid-positive patients. These events included venous thrombosis, stroke, myocardial infarction, gangrene, recurrent pregnancy loss and thrombocytopenia [20].

In our study, there was one patient from the seven patients who showed manifestations of VTE has abnormality in anti-cardiolipin level, while in **Wang *et al.*** [21] the percentage of patients had abnormality in anti-cardiolipin level and complain from VTE was 5.3%.

Finally, we found that seven donors showed manifestations of venous thromboembolism; 4 have multiple risk factors for thrombosis so presence of multiple risk factors for venous thromboembolism led to increase its incidence.

CONCLUSION

The presence of multiple risk factors for venous thromboembolism led to increase in its incidence, so during preoperative assessment of the donors, if they have multiple risk factors for thrombosis some precautions should be taken to avoid venous thrombosis.

Preoperative precautions included heamatological consultations for the donors and prophylaxis dose of anticoagulant. Intra operative precautions included pneumatic calf pressure, elastic stocking. Finally postoperative precautions should be continued , these donors should take therapeutic doses of anticoagulants and follow up by lower limb venous duplex.

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