Incidence of De Novo Hypertension in Patients Undergoing Living Donor Liver Transplantation and its Relation to the Type of Immunosuppression (Retrospective Study)

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Abstract: Background: Hypertension is a common problem after liver transplant occurring in 55-85%. Hypertension is a risk factor for ischemic heart disease, peripheral vascular disease, renal failure and death. Objectives: This was a retrospective study to determine the incidence of de novo hypertension in patients undergoing living transplantation from a living donor. Our second objective was to compare the effect of different calcineurin inhibitors on the incidence of de novo hypertension. Methods: This was a retrospective study that included 98 adult patients whom had passed 6 months after undergoing living donor liver transplantation, the included patients all didn't have pretransplant hypertension this was an exclusion criterion. Results:From the 98 patients included in the study, age range was 37-62 years with a median age of 44 years. The study also included 71 males and 27 females. Five patients (5.1%) had temporary or transient hypertension which has resolved within the first 2-6 months with follow up or treatment that has been withdrawn and no subsequent development of hypertension. Within the studied group 34 (34.7%) patients developed hypertension after liver transplantation. Patients who had de novo hypertension were divided into 2 groups; one group who received ciclosporine and the other group who received tacrolimus. In the group which used tacrolimus; the incidence of de novo hypertension was 39.4%, while the group in which ciclosporine was used; the incidence of de novo hypertension was 42.86% (P>0.05) (non-significant). Conclusion: The incidence of de novo hypertension is 34.7% in patients undergoing LDLT. The incidence of de novo hypertension is 40.4% in patients undergoing LDLT. In this study there was no statistically significant difference in the effect of either neoral nor FK in the occurrence of de novo hypertension in patients undergoing living donor liver transplantation.

[Wael Safwat, Rasha Refea, Medhat Abdel Aal, Ibrahim Mostafa and Mahmoud El Meteini. Incidence of De Novo Hypertension in Patients Undergoing Living Donor Liver Transplantation and its Relation to The Type of Immunosuppression (Retrospective Study)]. Nature and Science 2011; 9(7):99-101]. (ISSN: 1545-0740). http://www.sciencepub.net

Keywords: Living donor liver transplantation – De Novo hypertension –immunosuppression.

1. Introduction:

Hypertension is a common problem after liver transplant occurring in 55-85%.(1-4) Hypertension is a risk factor for ischemic heart disease, peripheral vascular disease, renal failure and death. Cyclosporine and less commonly, tacrolimus, cause hypertension by inducing vascular constriction of afferent renal arterioles, impairing glomerular filtration and sodium excretion. The mechanism has not been elucidated but may be caused by changes in the calcium efflux from smooth muscle cells or reduced prostacyclin or nitric oxide production. Steroids also increases the risk of hypertension, by producing hypervolemia. Steroid withdrawal may be the most important first step in the management of post-transplant hypertension. Because of the morbidity associated with hypertension, our goal is to keep the blood pressure below 140/90, and <130/85 in diabetics (5). Several classes of drugs are effective in treating hypertension in the post-liver transplant patient. Cyclosporine and tacrolimus may predispose to salt and water retention, so diuretics may be used in persons with edema (6-7). Cyclosporine and tacrolimus cause vasoconstriction so direct vasodilators such as calcium channel blockers (amlodipine, isradipine, felodipine, nifedipine) are a good first choice. Alternatives are indirect vasodilators that decrease sympathetic activity (clonidine and doxazosin). All of these medications can cause headache and fluid retention. NIcardipine, diltiazem and verapamil have limited use and can cause increased cyclosporine and tacrolimus levels. Clonidine and doxazosin both may cause sedation. Beta-blockers can be used and may also be helpful in prophylactic treatment of headaches caused by cyclosporine and tacrolimus. Angiotensin-converting enzymes (ACE) inhibitors are not useful immediately after liver transplant because renin levels decrease in the correction of cirrhosis. Hyperkalemia and renal insufficiency can be aggravated. However, ACE inhibitors may be preferable later, if patients have diabetic nephropathy. Losartin, an angiotensin II receptor antagonist, may be useful later post-transplant as well since cyclosporine upregulates angiotensin II receptors(8).

Objectives:

This was a retrospective study to determine the incidence of de novo hypertension in patients undergoing living transplantation from a living donor. Our second objective was to compare the effect of different calcineurin inhibitors on the incidence of de novo hypertension.

2. Methods:

This was a retrospective study that included 98 adult patients whom had passed 6 months after undergoing living donor liver transplantation, the included patients all didn't have pretransplant hypertension this was an exclusion criterion. All our patients had steroids which was graduall y tapered during the first 3 months as well as calcineurin inhibitor in addition to mycophenolate mofetil in most patients. The grade of hypertension was Based on recommendations of the Seventh Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)(9), the classification of blood pressure (expressed in mm Hg) for adults aged 18 years or older is as follows: Normal - Systolic lower than 120, diastolic lower than 80 . Prehypertension - Systolic 120-139, diastolic 80-99. Stage 1 - Systolic 140-159 or diastolic 90-99. Stage 2 - Systolic equal to or more than 160 or diastolic equal to or more than 100. Stage 3 > 180/110. Based on the average of 2 or more readings taken at each of 2 or more visits after initial screening. The treatment regimens were the initial use of calcium channel blocker followed by the addition or change of drug if the first drug is not tolerated or was contraindicated or showed evidence of side effects, the second drug used was beta-blockers, and the third drug was angiotensin converting enzyme inhibitor. Diuretics use was not preferred except for limited period of time in patients with edema.

3. Results:

From the 98 patients included in the study, age range was 37-62 years with a median age of 44 years. The study also included 71 males and 27 females. Five patients (5.1%) had temporary or transient hypertension which has resolved within the first 2-6 month with follow up or treatment that has been withdrawn and no subsequent development of hypertension. Within the studied group 34 (34.7%) patients developed hypertension after liver transplantation. Staging of hypertension was stage I in 21 (21.4%) patients and stage II in 13 (13.3%) patients and none of the patients had stage III hypertension. However one (1.02%) patient had severe resistant hypertension which was non-responding to treatment (stage II) and eventually responded to multi-drug regimen and one (1.02%) patient died due to cerebral hemorrhage due to non-adherence to his treatment. All patients started treatment of de-novo post liver transplant with calcium channel blockers with increasing doses till control of blood pressure, those who were not controlled 12 (12.2%) had another drug added for proper control of hypertension. All patients with proper adherence to treatment were controlled regarding their hypertension. Patients who had de novo hypertension were divided into 2 groups; one group who received ciclosporine and the other group who received tacrolimus. In the group which used tacrolimus; the incidence of de novo hypertension was 39.4%, while the group in which ciclosporine was used; the incidence of de novo hypertension was 42.86% (P>0.05) (non-significant). Among patients with need for antihypertensive drugs, the first choice was calcium channel blocker and controlled hypertension in 18 (52.9%) patients in those with de novo hypertension, meanwhile12 (35.3%) patients needed 2 drugs with the addition of a beta-blocker agent with a calcium channel blocker, and only 4 patients (11.8%) needed the addition of a third drug mostly an angiotensin converting enzyme inhibitor. The use of a single drug or more was not proportional with the stage of hypertension, as some patients with stage 1 needed more than one drug and some with stage 3 were controlled on a single drug regimen, however this was not statistically significant (P>0.05).

4. Discussion:

Clinical hypertension to levels greater than 140/90mm Hg is common within the first months after liver transplantation. Depending on the intensity of TAC or cyclosporine administration and the levels of corticosteroids used, arterial pressure increases to hypertensive levels (140/90 mm Hg, or a mean arterial pressure 107 mm Hg) during the first weeks to months in 50% to 75% of the liver transplant recipients (8). The rate of blood pressure elevation and the intensity of treatment required have decreased in recent years. In part, this may reflect the transition in immunosuppression protocols and the rapid reduction (and/or discontinuation) of steroids(5). The incidence of post LDLT seems to have an incidence of only 34.7% are mostly to the fact of using corticosteroids in lower doses which is lowered gradually to be discontinued within the first 3 months after LDLT. Another factor may be the restricted use in salt intake to all our patients specially that they don't receive Azathioprine as a part of the immunosuupression regimen, and that was stated in a study by Sodium sensitivity is a major feature of posttransplantation hypertension with calcineurin inhibitors. Early studies indicated that dietary sodium restriction led to a decrease in blood pressure during cyclosporine immunosuppression that was not observed during

azathioprine- based immunosuppression (10). Moerover previously published reports stated that LDLT needs lower levels of immunosuppressiion thatn that of cadaveric liver transplantation (11) hence this might explain the lower rates of de novo post LDLT hypertension in our studied group due to lower mean levels of calcineurin inhibitors. Moreover that with more time the need for multidrug regimens and the antihypertensive drug dosings are decreased. Non of our studied group had any cardiovascular events except for one death from a cerebrovascular stoke due to non-adherence to antihypertensive drugs for few weeks. Otherwise almost all our patients are strictly controlled regarding their De-novo post LDLT hypertension. Concerning the difference in the type of calcineurin inhibitor used and it's effect on the development of De-novo hypertension earlier reports stated that hypertension frequently develops early after liver transplantation when cyclosporine-based immunosuppression is used. However, initial experience with tacrolimus has suggested that its use leads to a lower early incidence of hypertension. Hypertension is associated with increased body weight in cyclosporine-treated patients and with more severe renal dysfunction in patients receiving tacrolimus (12). However in this present study and although the incidence of de-novo hypertension was 39.4% with tacrolimus versus 42.8% with cyclosporine this difference was not statistically significant for the 2 drugs, we think that again this may be to the fact of the use of generally lower mean levels of calcineurin inhibitors, the avoidance of use of Azathioprine in the immunosuppresion regimens in our center and the early gradual withdrawal of steroids within the first 3 month. The development of De-novo hypertension after liver transplantation, although lower in cases with LDLT (34.7%) as compared to (55-85%) after OLT is still a major concern for long term morbidity after successful liver transplant and care must be exercised for diagnosis, treatment initiation and proper follow up for best care provision for our patients.

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6/2/2011