ORIGINAL ARTICLE

The use of Valsartan in hypertensive renal transplant recipients

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The aim of this study was to investigate the efficacy and safety of valsartan in the treatment of hypertension in patients with renal transplantation. Twenty three patients (18 men) on therapy with antihypertensive drugs were included in the study because of insufficient control of their blood pressure and/or drug side effects. These patients received valsartan at the dose of 80-160 mg/d. All patients in the study had serum creatinine level < 2.0 mg/dl before treatment with valsartan and a follow up six months before and six months after treatment. Systolic (SBP) and diastolic blood pressure (DBP), serum creatinine (Scr), Ht, Hb, uric acid and potassium were recorded every two months for a period of six months before (BVT) and six months after initiation of valsartan treatment (AVT). Proteinuria, number of antihypertensive agents, cyclosporine (CsA) dose and levels were recorded BVT (time 0) and six months later. Two patients stopped valsartan treatment because of serum creatinine elevation. ANOVA for repeated measures and paired t test were used for statistical analysis.

SBP/DBP was 142.63±12.51/89.47±8.48 mmHg, 142.63±17.74/88.42±6.67 mm Hg, 144.47± 11.53/ 92.63 ± 8.22 mmHg, 151.05± 11.37/89.47±7.61 mmHg 6, 4, 2 and 0 months BVT respectively (p=NS) and 142.00 ± 9.92/ 85.25±6.78 mmHg, 137.25±10.93/85.75±6.72 mmHg and 133.25±8.92/84.00±5.92 mmHg 2, 4 and 6 months AVT respectively (p=0.0001 for SBP). The number of antihypertensive agents per patient was 2.09±0.83/1.47±0.60(p=0.001) at time 0 and six months after valsartan initiation. Scr was 1.30±0.34 mg/dl, 1.29±0.32 mg/dl, 1.31±0.33 mg/dl and 1.28±0.33 mg/dl 6, 4, 2 and 0 months BVT, respectively (p=NS) and 1.36±0.36 mg/dl, 1.40±0.37 mg/dl and 1,34±0.32 mg/dl 2, 4 and 6 months AVT initiation respectively (p=0.036). Ht/Hb were 40.47± 6.26%/13.13±2.07g/dl, 40.78 ± 6.39% /13.01 ±2.03g/dl, 41.21±5.98% /13.22 ± 2.01g/dl, 41.77±6.04%/ 13.32 ± 2.02 g/dl 6, 4, 2 and 0 months BVT respectively (p=NS) and 38.65±6.10% / 12.65 ±1.93 g/dl, 38.65±6.10%/ 12.51±2.01 g/dl, 38.10±5.77%/12.55±2.10g/dl at 2, 4 and 6 months AVT initiation, respectively (p=0.001/ 0.022 respectively).

In conclusion Valsartan offers a better control of blood pressure in patients with renal transplantation, lowers significantly the number of antihypertensive agents needed, causes a significant fall of Ht/Hb and a small but significant rise of serum creatinine level.
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Hypertension occurs in about 70%-90%[1-4] of patients with renal transplantation. Rejection, immunosuppressive agents, recurrent renal disease, renal artery stenosis, native kidney disease, polycythemia, weight gain and renal failure are the best known causes of post-transplantion arterial hypertension [3-6]. Post transplantation arterial hypertension has been associated recently with reduced kidney graft survival [7-10] and the best management of it is not known. The drugs preferred for the treatment of hypertension of renal transplant recipients are

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calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors and recently angiotensin II type I receptor antagonists[11].

Angiotensin II antagonists act selectively and competitively to angiotensin II receptor type I (AT1RA). These drugs may have the benefits of ACE inhibitors (lower both the systematic and intraglomerular pressure resulting in a decrease of glomerular hypertension, reduction of proteinuria and increase in renal functional reserve)[12] without the adverse effects induced by bradykinins[13], but their long term effect on blood pressure and renal function have not been analysed.

The first of these drugs that was used in clinical practice, losartan, has been shown to be safe and effective in the middle and short term treatment of hypertension in transplanted patients[11,14]. The effectiveness of AT1RA may be influenced by receptor affinity, pharmacokinetic properties and access of the active drug to the sites of action. Valsartan, a second generation AT1RA, has a 5-fold greater affinity for the receptor than losartan and it does not bind to other sites, like losartan[15]. Losartan has no steady biotransformation, it is metabolized by the cyp 450 isoform 3A4 and may be influenced by drugs such as cyclosporine A, antifungal agents, statins, antibiotics etc, while valsartan has no need to be metabolized to be effective, but its bioavailability is variable, depended on meals[16]. The elimination half life of valsartan is longer than that of losartan. Several trials have shown that valsartan can be given in patients with renal failure with a good safety and tolerance profile comparable to placebo[16-18].

The aim of this study was to investigate the safety and efficacy of valsartan on blood pressure, renal function and proteinuria in a group of hypertensive renal transplant recipients with normal graft function.

Patients and Methods

Twenty three patients with renal transplantation and arterial hypertension were selected to receive valsartan treatment in an outpatient basis at Hippokrateio General Hospital of Thessaloniki. They were 40.91±14.15 year old (range 18-61), on triple (14) or quadruple sequential immunosuppression (9) and had received a graft from living related donor (LRD) (12 cases) or a cadaveric (CD) graft (11 cases). The demographic data of patients are shown in table 1.

Table 1. Demographic data

Male/female	18/5
Mean age (years)	41(range 18-61)
Primary renal disease	
Glomerulonephritis	11
Interstitial nephritis	3
Polycystic kidneys	3
Hypertensive glomerulopathy	2
Unknown etiology	4
Inclusion criteria	
Uncontrolled BP	14
Erythrocytosis	4
Leg oedema – gum hypertrophy	5

There were no patients with serum creatinine 2.0 mg/dl or more, salt depletion, any active disease at the time of drug initiation or documented renal artery stenosis. Valsartan was given because of systolic blood pressure (SBP) > 140 mmHg and / or diastolic blood pressure (DBP) > 90 mmHg in two or more readings performed at different days or because of a clinical condition causing considerable discomfort (erythrocytosis, leg edema, gum hypertrophy). The conventional antihypertensive drugs were stopped 24 hours before valsartan initiation. Valsartan was given 4.20±3.11 years after transplantation. The initial dose was 80 mg/d. In cases of inadequate control of blood pressure after fifteen days treatment, the dose was doubled and after that a second drug was added if it was necessary. The blood pressure was measured at sitting position, always with the same auscilometric machine. Blood pressure measurements and blood and urine samples were taken, on outpatient basis, 6, 4, 2 months before valsartan initiation, at starting point and 2, 4 and 6 months after valsartan initiation. Serum creatinine, Ht, Hb, uric acid and potassium were measured regularly. Proteinuria (24 hour urine protein output) and cyclosporine levels were recorded on valsartan initiation and six months later. The number of antihypertensive drugs, valsartan dose and cyclosporine levels were measured at time 0 and six months later.

ANOVA for repeated measures was used to examine the value change during time. Student's t test was used to compare quantitative variables

Table 2. Levels of systolic and diastolic blood pressure measured at bimonthly intervals before and after initiation of valsartan treatment (mmHg)

Months	-6	-4	-2	0	+2	+4	+6
SBP	149.63±12.51	142.63±17.74	144.47±11.53	151.05±11.37*	142.00±9.92*	137.25±10.93*	133.25±8.92*
DBP	89.47±8.48	88.42±6.67	92.63±8.22	89.47±7.61	85.25±6.78	85.75±6.72	84.00±5.92

ANOVA for repeated measures *p:0.0001

Table 3. Proteinuria, number of antihypertensive drugs, valsartan dose, cyclosporine levels and dose at the initiation of treatment and six months later

	treatment initiation	6 months later
24 hour urine protein(g) (7 patients)	0.85±0.99	0.68±0.86
number of antihypertensive drugs	2.09±0.83*	1.47±0.60*
valsartan dose(mg/d)	91.42±28.68	95.23±32.18
cyclosporine levels(μg/l)	101.75±71.95	86.62±36.54
cyclosporine dose (mg/d)	158.33±75.96	145.23±65.00

paired t test *p:0.001

Table 4. Mean values of serum creatinine, Ht and Hb measured at bimonthly intervals before and after initiation of valsartan treatment

Months	-6	-4	-2	0	+2	+4	+6
Serum creatinine (mg/dl)	1.30±0.34	1.29±0.32	1.31±0.33	1.28±0.33[1]	1.36±0.36[1]	1.40±0.37[1]	1.34±0.32[1]
Ht (%)	40.47±6.26	40.78±6.39	41.21±5.98	41.77±6.04[2]	38.65±6.1[2]	38.65±6.1[2]	38.1± 5.77[2]
Hb (g/dl)	13.13±2.07	13.01±2.03	13.22±2.01	13.32±2.02[3]	12.65±1.93[3]	12.51±2.01[3]	12.55±2.1[3]

ANOVA for repeated measures [1]p:0.036, [2]p:0.001, [3]p:0.022

Table 5. Mean values of serum potassium and uric acid levels measured at bimonthly intervals before and after initiation of valsartan treatment

Months	-6	-4	-2	0	+2	+4	+6
Uric Acid	7.05±1.84	7.44±1.78	7.37±1.51	7.28±1.24	7.25±1.15	7.36±1.40	7.37±1.20
Potassium	4.47±0.38	4.52±0.49	4.37±0.39	4,40±0.43	4.70±0.46	4.62±0.43	4.74±0.50

ANOVA for repeated measures p:NS

at time 0 and six months later after treatment initiation. Regression analysis for curve estimation was used to examine the slope of serum creatinine before and after valsartan initiation. A value of $p < 0.05$ was considered to be significant. Quantitative results were expressed as Mean±SD. The statistical package SPSS for windows, version 10.0, was used.

Results

Two patients were withdrawn from the study because there was a serum creatinine elevation of more than 0.5 mg/dl in the first fifteen days of treatment. The drug was stopped and serum creatinine levels came back to baseline levels. Investigation for renal artery stenosis was negative, there was no dehydration or diuretic consumption. The SBP of our patients showed a statistically significant (ss) fall after valsartan initiation (table 2, Figure 1) and the number of antihypertensive drugs necessary to control the blood pressure fell statistically significantly (table 3). The antihypertensive agents that were substituted by valsartan were : calcium channel antagonists, ß-adrenergic blockers, clonidine and minoxidil. Valsartan initial mean dose and 24 hour urine protein output at the beginning of therapy did not differ significantly from the values recorded six months later (table 3). Tachycardia, orthostatic hypotension or syndrome were not

recorded. Side effects such as cough, angioneurotic edema or dysgeusia were not noticed.

Forty four out of 79 readings of blood pressure, during the six month time before valsartan initiation, recorded SBP > 140 mmHg and 18 out of 79 readings recorded DBP >90 mmHg (frequency 55.69% and 26.58% respectively). Twenty one out of 62 readings of blood pressure of the same patients, at the six month period after valsartan initiation, recorded SBP >140 mmHg and four out of 62 readings disclosed DBP >90 mmHg (frequency 29.03% and 6.45% respectively).

Mean serum creatinine levels increased by 0.06 mg/dl during the six month period after valsartan initiation but this small change was statistically significant (table 4). In figure 2 the curve of mean serum creatinine levels during time is shown (p:NS, slope : 0.01).

Hematocrit and Hb showed 8.78% and 5.78% decrease respectively six months after valsartan initiation. This decrease was noticed in the first two months after valsartan initiation and remained stable for the rest of the follow up period (table 4, figure 3).

Analysis of uric acid and potassium serum levels did not show any difference before and after initiation of valsartan treatment (table 5). No case of hyperkalemia was identified during the six month follow up after initiation of valsartan treatment.

Cyclosporine dose and levels measured at the initiation of valsartan treatment and six months later did not show any statistically significant difference (table 3).

Patients with erythrocytosis (Ht ≥ 50%) at the end of follow up had their Ht in the normal range. Also there was remission of leg edema and gum hypertrophy.

Discussion

Hypertension is an important risk factor for cardiovascular morbidity and mortality. It also affects the progression of renal failure. Thus, long term control of high blood pressure is required. The optimum management of transplant hypertension remains to be defined and requires individualization. Calcium channel blockers are currently the drugs of choice in hypertensive renal transplant recipients, able to reverse cyclosporine induced renal vasoconstriction[19]. On the basis of their renoprotective mechanisms, treatment with ACE inhibitors have been recommended although many physicians avoid this drug category because a functional decrease of renal perfusion when administered with CsA[20].

Sympathetic overactivity, as it happens in congestive heart failure, leads to increased formation and release of renin through activation of ß-adrenoceptors by noradrenaline[21]. Angiotensin II production by this way will act back to activate presynaptic angiotensin II receptors and further enhance noradrenaline release[22]. Noradrenaline is proarrhythmic factor, leads to ß-adrenoceptor downregulation and has growth promoting effects via α and ß adrenoceptors[23]. Moreover long lasting sympathetic overactivity is injurious to the kidney at least when renal disease is present[24].

ACE inhibitors in concentrations that effectively lower blood pressure fail to completely block local angiotensin II mediated effects on noradrenaline release[25] and enhance bradykinine levels[26]. Ang II receptor blockers block Ag II mediated noradrenaline release and do not interfere with bradykinine degradation[27].

Intrarenal renin-angiotensin system is significant for the growth, sclerosis and regulation of heamodynamics of the glomerulus[28]. TGF-ß1, connected with the Ang II production, is considered to be a significant fibrogenic factor implicated in a number of chronic diseases of the kidney[29]. Furthermore, the osteopontin inhibition by valsartan in a rat model with subtotal nephrectomy has been connected with reduction in macrophage infiltration and tubulointerstitial injury[30]. The proof that AT1RA could decrease synthesis and activation of TGF-ß1 and blockade osteopontin expression further supports the idea that these drugs could be useful in the treatment of hypertension in renal transplant recipients[31].

Until now, AT1RA therapy is used with causion in patients with renal allografts. Although the first results with losartan therapy are encouraging (better pressure control-reduction of proteinuria), no information is available whether treatment with AT1RA might exert a positive effect on the long term graft survival and chronic allograft nephropathy. In our study valsartan therapy resulted in better blood pressure control in this group of transplanted patients compared to the conventional antihypertensive drugs used previously (table 2

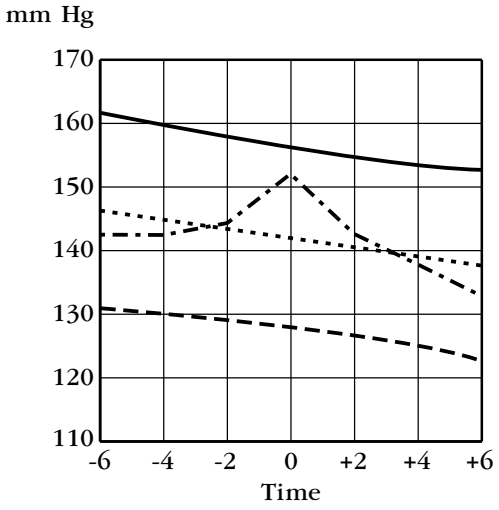

Figure 1

Systolic blood pressure
Fit for mean SBP level
95% LCL* for SBP
95% UCL** for SBP

* LCL: Lower curve levels
** UCL: Upper curve levels

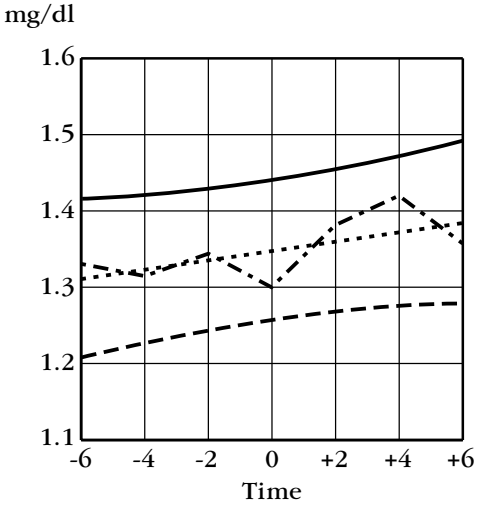

Figure 2

Serum creatinine
Fit for mean SERCR level
95% LCL for SERCR
95% UCL for SERCR

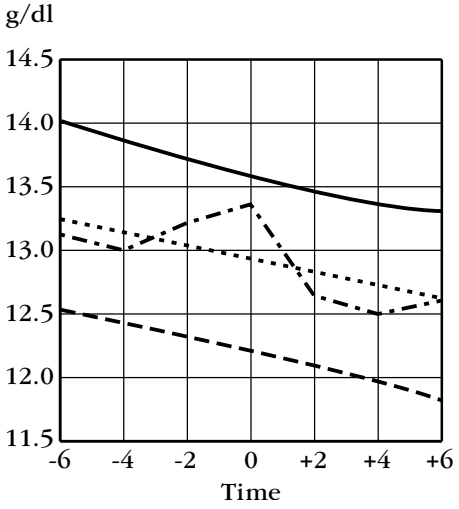

Figure 3

Haemoglobin levels
Fit for mean HAEM level
95% LCL for HAEM
95% UCL for HAEM

and 3) and this is due to the decrease of intrarenal and systemic arterial resistance[13].

The decrease of proteinuria was not ss but we already know that this was due to the small number of patients[14,32,33]. AT1RA and ACE inhibitors[34] seem to exert the same favorable effect in proteinuric renal transplant recipients.

The better arterial blood pressure control was accompanied by a reduction or disappearance of unwanted side effects encountered before treatment (erythocytosis, leg edema and gum hypertrophy).

It has been reported a 10% decrease in GFR in patients taking ACE inhibitors or AT1RA[25]. In our study graft function, as it was shown by serum creatinine levels, was negatively influenced, possibly because of changes in glomerular dynamics resulting in a decrease of GFR. The same observations were reported by De Castillo et al, who used losartan in their study[14]. In spite the fact that mean serum creatinine change was not clinically significant, this finding merits further investigation during time to establish whether the use of this drug causes an abrupt fall of graft function which is then stabilized. The investigation with renal angiography in two cases with acute fall of renal function did not disclose stenotic lesions in renal artery. A possible explanation is the existence of intrarenal vessel atheromatosis.

Stimulation of AT1 receptors of erythroid progenitor cells by angiotensin II is believed to increase red cell mass independently from circulating erythropoietin[35]. In our study a statistically significant fall of Ht and Hb was noticed as early as the second month of treatment. Ht and Hb levels remained stable for the rest of the follow up. This finding suggests that the blockade of AT1 receptors results in a decrease of red blood cell mass independently of erythropoietin and haemoglobin levels[36].

Cough is the most common side effect of angiotensin converting enzyme inhibitors with an incidence estimated at 5% to 20%[37]. We did not notice cough in our study and this is in agreement with previous works[11,38]. Our finding supports the hypothesis that the cough is mediated by bradykinine. Another side effect of ACEI is the angioneurotic edema that has been noticed in about 0.1% of treated patients. Our patients did not present angioneurotic edema but it has appeared occasionally in patients taking other AT1RA[39]. Other side effects, such as tachycardia (>100 beats/min), orthostatic hypotension and dysgeusia, were not noticed in our patients. The lack of tachycardia is probably due to simultaneous reset of baroreflexes by the drug[40].

ACE inhibitors preserve or increase serum potassium levels[41,42] and can cause hyperkalemia if they are given to patients taking CsA[43]. In our study potassium levels increased but not significantly and hyperkalemia was not observed (table 5) in spite the fact the patients were taking CyA[18]. Analogous findings have been reported for losartan[11,14], therefore we can not incriminate the way of metabolism of these drugs.

It has been reported that valsartan and cyclosporine present pharmacokinetic interaction[44]. In our study cyclosporine levels did not change during valsartan treatment (table 3) and possibly this is due to the fact that valsartan is not metabolized in the liver as it happens with cyclosporine and losartan which have the 3A4 enzyme system as their common pathway of metabolism.

Keeping in mind that valsartan does not seem to raise cyclosporine levels, reduces ss systolic blood pressure and decreases the need for other antihypertensive agents it is justified to use this drug on a chronic basis and further evaluate it in hypertensive renal transplant recipients with or without long term complications. Special attention must be paid during the first fifteen days of treatment to possible elevation of serum creatinine levels in which case treatment with valsartan should be stopped immediately.

ΠΕΡΙΛΗΨΗ

Γ. Βέργουλας, Γρ. Μυσερλής, Δ. Γάκης, Θ. Ατματζίδης, Α. Αντωνιάδης. **Η χρήση της βαλσαρτάνης στη θεραπεία της υπέρτασης ασθενών με νεφρικό μόσχευμα.** Ιπποκράτεια 2001, 5 (2): 61-68

Σκοπός αυτής της μελέτης ήταν η διερεύνηση της ασφάλειας και της αποτελεσματικότητας της βαλσαρτάνης στη θεραπεία της υπέρτασης ασθενών με νεφρική μεταμόσχευση. Στη μελέτη περιλήφθηκαν είκοσι τρεις ασθενείς (18 άνδρες) που βρίσκονταν σε αντιυπερτασική αγωγή διότι η πίεσή τους δεν ελέγχονταν καλά ή παρουσίαζαν ανεπιθύμητες ενέργειες των φαρμάκων. Οι ασθενείς αυτοί έλαβαν βαλσαρτάνη στη δόση των 80-160 mg/d. Όλοι τους είχαν κρεατινίνη ορού < 2.0 mg/dl πριν από τη θεραπεία με βαλσαρτάνη

και παρακολούθηση έξι μήνες πριν και έξι μήνες μετά τη χορήγηση του φαρμάκου. Η Συστολική (SBP) και η διαστολική αρτηριακή πίεση (DBP), η κρεατινίνη ορού (Scr), ο Ht, η Hb, το ουρικό οξύ και το κάλιο καταγράφηκαν κάθε δύο μήνες για διάστημα έξι μηνών πριν (BVT) και έξι μετά την έναρξη θεραπείας με βαλσαρτάνη (AVT). Η λευκωματουρία, ο αριθμός των αντιυπερτασικών παραγόντων, η δόση και τα επίπεδα της κυκλοσπορίνης (CsA) καταγράφηκαν BVT (χρόνος 0) και έξι μήνες αργότερα. Δυο από τους ασθενείς σταμάτησαν τη θεραπεία με βαλσαρτάνη διότι ανέβηκε η κρεατινίνη του ορού. ANOVA για επαναλαμβανόμενες μετρήσεις και t test για ζεύγη τιμών χρησιμοποιήθηκαν για τη στατιστική ανάλυση των αποτελεσμάτων.

Η SBP/DBP ήταν 142.63±12.51/89.47±8.48 mmHg, 142.63±17.74/88.42±6.67 mm Hg, 144.47±11.53/ 92.63 ± 8.22 mmHg, 151.05± 11.37/89.47±7.61 mmHg 6, 4, 2 και 0 μήνες BVT, αντίστοιχα (p=NS) και 142.00 ± 9.92/85.25±6.78 mmHg, 137.25±10.93/85.75±6.72 mmHg και 133.25±8.92/84.00±5.92 mmHg 2, 4 και 6 μήνες AVT, αντίστοιχα (p=0.0001 για SBP). Ο αριθμός των αντιυπερτασικών φαρμάκων ανά ασθενή ήταν 2.09±0.83/1.47±0.60(p=0.001) πριν και έξι μήνες μετά την έναρξη της βαλσαρτάνης. Η Scr ήταν 1.30±0.34 mg/dl, 1.29±0.32 mg/dl, 1.31±0.33 mg/dl και 1.28±0.33 mg/dl 6, 4, 2 και 0 μήνες BVT, αντίστοιχα (p=NS) και 1.36±0.36 mg/dl, 1.40±0.37 mg/dl και 1,34±0.32 mg/dl 2, 4 και 6 μήνες AVT έναρξη αντίστοιχα (p=0.036). Ht/Hb ήταν 40.47± 6.26% /13.13 ±2.07 g/dl, 40.78 ± 6.39% /13.01 ±2.03g/dl, 41.21±5.98% /13.22 ± 2.01g/dl, 41.77 ± 6.04%/13.32±2.02g/dl 6, 4, 2 και 0 μήνες BVT αντίστοιχα (p=NS) και 38.65 ± 6.10%/12.65±1.93 g/dl, 38.65±6.10%/12.51±2.01 g/dl, 38.10±5.77% /12.55 ±2.10g/dl στους 2, 4 και 6 μήνες AVT έναρξη, αντίστοιχα (p=0.001/ 0.022 αντίστοιχα).

Συμπερασματικά η βαλσαρτάνη επιτυγχάνει καλύτερο έλεγχο της αρτηριακής πίεσης του αίματος σε ασθενείς με νεφρική μεταμόσχευση, ελαττώνει σημαντικά τον αριθμό των αντιυπερτασικών παραγόντων ανά ασθενή, προκαλεί σημαντική πτώση του Ht/Hb και μια μικρή αλλά ss άνοδο της κρεατινίνης του ορού.

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