Original Paper

Treatment of Hypertension in Renal Transplant Recipients in Four Independent Cross-Sectional Analyses

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Key Words

Kidney transplantation • Hypertension • Antihypertensive treatment • Beta-blocker • Calcium channel blocker

Abstract

Background/Aims: This retrospective study analysed hypertension management and adherence to blood pressure (BP) targets among renal transplant recipients (RTRs) under specialized care in the Outpatient Transplantation Unit in the Department of Nephrology, Transplantology and Internal Medicine at Gdansk University Hospital. **Methods:** Medical records of 101, 316, 639 and 818 RTRs diagnosed with hypertension, who received outpatient care in 2001, 2006, 2011 and 2014, respectively were analysed in four independent cross-sectional surveys. All RTRs received antihypertensive regimens. **Results:** The overall most commonly used antihypertensive agents were beta-blockers (BB) (range 66.3-82.5%) followed by calcium channel blockers (CCB) (range 52.8-64.2%). Whilst a significant, upward tendency of BB usage ($p < 0.01$) was observed, CCB usage ($p < 0.001$) displayed a downward tendency as a first line therapy in the subsequent years. The average number of antihypertensive agents used per patient increased significantly from 2.24 ± 1.03 in 2001 to 2.55 ± 1.25 in 2014 ($p < 0.05$). The most frequently used combination of hypotensive therapy consisted of two or three antihypertensive drugs depending on the survey. The most common two drug combination consisted of BB and CCB followed by BB accompanied by angiotensin converting enzyme inhibitors. A significant, upward tendency in the use of four ($p < 0.001$) and five ($p < 0.05$) antihypertensive drugs simultaneously, was observed in subsequent years.

The target values of BP i.e. <140/90 mmHg were accomplished in 47, 58, 60 and 46% of RTRs in subsequent years. In a secondary - stratified analysis of data from 2014, younger patients ($p<0.05$), patients with better graft function ($p<0.001$), patients treated with a higher number of antihypertensive agents ($p<0.001$) and those not treated with BB ($p<0.01$) were shown to reach the BP target of below 140/90 mmHg more often. **Conclusion:** The study showed intensification of hypertension treatment in RTRs in subsequent years with BB assuming a dominant role.

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Introduction

Hypertension is one of the most common clinical problems seen in renal transplant recipients (RTRs). The overall prevalence, defined as the use of antihypertensive agents with or without elevated blood pressure (BP), has been reported to be as high as 85% [1]. It is generally accepted that hypertension negatively influences kidney transplant outcomes. The Collaborative Transplant Study, a large cohort study of nearly 30,000 RTRs, showed a graded association between both systolic and diastolic BP and allograft failure [2]. In addition to decreased allograft survival, post-transplantation hypertension is associated with decreased patient survival. Each 10-mmHg increment of systolic BP >140 is associated with a hazard ratio of death of 1.18 (95% CI, 1.12 to 1.23), and this risk persists after adjusting for allograft function [3]. Despite the high awareness of hypertension and large number of studies concentrated on this issue, only a few of them evaluate the management of hypertension and adherence to guidelines in RTRs. We therefore, performed this study to analyse hypertension management and control rates among RTRs in the last 15 years.

Materials and Methods

The aim of the study was to assess the management of hypertension at four different time points, and evaluate adherence to BP targets recommended for RTRs. Hypertension was defined as systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg, or currently undergoing antihypertensive treatment. BP was considered to be controlled if systolic BP was < 140 mmHg and diastolic BP was < 90 mmHg. Adult RTRs with arterial hypertension were the subjects of the study. Four cross-sectional, retrospective analyses were performed in the Outpatient Transplantation Unit in the Department of Nephrology, Transplantology and Internal Medicine at Gdansk University Hospital, Poland. Data was collected from January 2014 to November 2014. The authors analysed 894 medical records of adult RTRs treated in the unit. The first survey analysed the data of patients treated in the unit in 2001, the second, third and fourth surveys covered the years 2006, 2011 and 2014, respectively. The analysis concerned data from the first visit in a particular year, and it included the following demographic status and clinical information: sex, age, the cause of end stage renal disease (ESRD), systolic and diastolic BP recorded in the office during this visit, current treatment and data related to renal, diabetic and cardiovascular status of the patients.

In a secondary analysis, RTRs treated in 2014, were stratified according to eGFR, age, gender, cardiovascular complications and/or diabetes presence, pre-emptive transplantation, immunosuppression with cyclosporine or tacrolimus, number of antihypertensive agents, therapy with angiotensin converting enzyme inhibitors (ACEI) and/or ARB, therapy with BB. Data was evaluated using a STATISTICA (version 12.0 Stat Soft Inc.) software package. The variables are expressed as mean value $\pm$ standard deviation (SD), numbers or frequencies (percentages). The Chi square (χ^2) test was performed in order to measure the differences between selected categories. The quantitative variables were assessed by analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test. A $p<0.05$ was considered statistically significant.

Table 1. The characteristics of the study population. KTRs – Kidney Transplant Recipients, HA – hypertension, sCr – serum creatinine, KTx – kidney transplantation, eGFR – estimated glomerular filtration rate, BMI – body mass index, ESRD – end stage renal disease

Characteristics	2001	2006	2011	2014
n (screened/KTRs with HA)	105/101	330/316	664/639	861/818
Preemptive (n/%)	0 (0)	11 (3.5)	37 (5.8)	49 (6)
Sex (F/M)	42/59	117/199	237/402	303/515
Age	56.5 ± 11.2	54.6 ± 12.8	53.4 ± 13.4	53 ± 13.7
sCr level (mg/dl)	1.49 ± 0.4	1.52 ± 0.7	1.39 ± 0.6	1.54 ± 0.6
eGFR CKD-EPI (ml/min/1.73m ²)	49 ± 12.98	52.7 ± 18.4	59.1 ± 20.4	53.4 ± 19.9
BMI (kg/m ²)	25.4 ± 3.7	25.3 ± 4.4	26.2 ± 6.9	28.8 ± 14.7
Cardiovascular disease (%)	14.8	17.7	19.8	21.5
Diabetes mellitus (%)	10.9	16.4	22.2	23.2
Reasons of ESRD and KTx:	n (%)			
- primary glomerulonephritis	52 (49.5)	133 (42.1)	235 (36.8)	272 (33.2)
- diabetic nephropathy	5 (4.9)	23 (7.3)	64 (10)	91 (11.1)
- hypertensive nephropathy	3 (2.9)	13 (4.1)	46 (7.2)	59 (7.2)
- polycystic kidney disease	8 (7.9)	27 (8.5)	61 (9.5)	82 (10)
- tubulointerstitial nephritis	8 (7.9)	41 (12.9)	70 (10.9)	80 (9.8)

Table 2. Percentage of RTRs receiving certain immunosuppressant. mTOR Inhibitors – Everolimus and Sirolimus

Year	2001	2006	2011	2014
Type of immunosuppressive drug:	n (%)			
Glucocorticosteroids	101 (100)	301 (95)	577 (90.3)	748 (91.4)
Cyclosporine A	91 (90.1)	288 (72.1)	313 (48.9)	334 (40.8)
Tacrolimus	7 (6.9)	74 (23.4)	312 (48.9)	463 (56.8)
mTOR inhibitors	0 (0)	19 (6)	30 (4.7)	45 (5.5)

Results

Characteristics of the study population

A total of 105, 330, 664 and 861 RTRs were screened in 2001, 2006, 2011 and 2014 respectively. 101, 316, 639 and 818 patients had hypertension and were included in the four independent surveys. The general characteristics of the analysed groups are presented in Table 1. The average age of RTRs decreased significantly in subsequent years from 56.5 years in 2001 to 53 years in 2014 ($p < 0.05$). There was also a significant, upward tendency in the average BMI ($p < 0.05$) and more patients had diabetes and cardiovascular comorbidities ($p < 0.05$). Furthermore, the percentage of patients suffering from primary glomerulonephritis as the main cause of ESRD ($p < 0.05$) subsequently decreased. In addition, there was a major difference in immunosuppressive therapy between the four populations. The analyses revealed a significant decrease in the use of glucocorticoids ($p < 0.05$) and cyclosporine A ($p < 0.001$), while the percentage of patients treated with tacrolimus ($p < 0.001$) and mTOR inhibitors peaked in subsequent years ($p < 0.05$) (Table 2).

Fig. 1. The antihypertensive drugs used by renal transplant recipients.

Antihypertensive treatment

Hypertension was diagnosed in 96.2, 95.7, 96.2 and 95% of screened patients respectively. All RTRs received antihypertensive regimens. The average number of antihypertensive agents used per patient increased significantly in successive years ($p < 0.05$) 2.24 ± 1.03 (2001), 2.55 ± 1.19 (2006), 2.56 ± 1.21 (2011) and 2.55 ± 1.25 (2014).

The most commonly used antihypertensive agents in 2014 were as follows: beta-blockers (BB) (80%), calcium channel blockers (CCB) (53%), diuretics (37%), alpha-blockers (35%), angiotensin-converting-enzyme inhibitors (ACEI) (32%) and angiotensin II receptor blockers (ARB) (7%). Detailed results of all the surveys are shown in Fig. 1. There was a significant trend towards greater use of alpha-blockers ($p < 0.001$), BB ($p < 0.001$) and diuretics ($p < 0.05$), simultaneously the number of patients receiving CCB decreased in subsequent years ($p < 0.001$). The overall use of agents inhibiting renin-angiotensin-aldosterone system i.e. ACEI and ARB increased significantly in 2006 and was stable between 2006-2014 in the range 43-49% (Fig. 1).

The most commonly used monotherapy antihypertensive agents were as follows: BB (34.6, 50.0, 67.7, 63.3%), CCB (42.4, 17.8, 13.5, 14.7%), diuretics (11.5, 17.9, 18.9, 9.3%) and ACEI (7.7, 17.8, 9.0, 7.3%). Whilst a significant, upward tendency of BB usage ($p < 0.01$) was observed, CCB usage ($p < 0.001$) showed a downward tendency as a first line therapy in the subsequent years. The most frequently used combination of hypotensive therapy consisted of two or three antihypertensive drugs (Fig. 2) in all the surveys. The most common two drug combination consisted of BB and CCB (48.6, 38.8, 34.9 and 36.03% in subsequent years) followed by BB combined with ACEI (11.4, 21.2, 25.5 and 17.1%). Moreover, a significant,

Fig. 2. Percentage of antihypertensive medications used by renal transplant recipients.

upward tendency in the use of four ($p<0.001$) and five ($p<0.05$) antihypertensive drugs simultaneously was observed in the subsequent years (Fig. 2).

Adherence to BP targets

The average systolic BP increased ($p<0.05$) while the average diastolic BP decreased ($p<0.05$) in subsequent years (Fig. 3). Overall, the target values of BP for the general population (i.e. $<140/90$ mmHg) were accomplished in 47, 58, 60 and 46% of patients in the subsequently analysed years. A significant improvement in BP control was observed between 2001 and 2011 ($p<0.05$), while deterioration was noticed between 2011 and 2014 ($p<0.001$) (Fig. 4).

The stratified bivariate analysis of hypertension control in 2014 by gender, age, eGFR, pre-emptive transplantation, immunosuppression with cyclosporine or tacrolimus, presence of diabetes and/or cardiovascular complications, number of antihypertensive agents, therapy with ACEI and/or ARB, therapy with BB, the cause of ESRD, showed that younger patients ($p<0.05$), RTRs with higher eGFR ($p<0.001$), subjects treated with a higher number of antihypertensive agents ($p<0.001$), those not treated with BB ($p<0.01$) more often reached the target BP of below $140/90$ mmHg (Table 3). The study also showed a negative association between diagnosis of primary glomerulonephritis or hypertensive nephropathy and BP control (Table 4).

Fig. 3. Mean systolic and diastolic blood pressure values in the groups.

Fig. 4. Percentage of renal transplant recipients who attained the blood pressure target $<140/90$.

Table 3. Bivariate associations with BP control (<140/90 mmHg). eGFR - estimated glomerular filtration rate, CVC - cardiovascular comorbidities, BB - beta blockers, ACEI - angiotensin converting enzyme inhibitors, ARB - angiotensin II receptor blockers, BP - blood pressure

Variables	BP controlled	BP not controlled	p value
Patients age, years	51.73 ± 14.42	53.58 ± 13.42	0.046
eGFR CKD-EPI, ml/min	60.6 ± 23.6	50.7 ± 19.2	< 0.001
Pre-emptive transplantation (%)			0.26
Yes	56.4	43.6	
No	48.6	51.4	
Patients gender (%)			1.0
Female	49.1	50.9	
Male	49.1	50.9	
Diabetes and/or CVC (%)			0.98
Yes	49.0	51.0	
No	49.1	50.9	
Immunosuppression (%)			0.09
Cyclosporine	49.8	50.2	
Tacrolimus	43.9	56.1	
Number of antihypertensive agents	2.43 ± 1.3	1.88 ± 1.5	< 0.001
Beta blockers (%)			0.007
Yes	43.9	56.1	
No	55.3	44.7	
ACEI and/or ARB (%)			0.08
Yes	57.1	42.9	
No	48.0	52.0	

Table 4. Bivariate analysis of the reasons for the ESRD in addition to BP control (<140/90 mmHg)

The reason of ESRD	BP controlled	BP not controlled	p value
Primary glomerulonephritis (%)	44.7	55.3	p<0.05
Diabetic nephropathy (%)	53.3	46.7	p=0.37
Hypertensive nephropathy (%)	33.9	66.1	p<0.001
Polycystic kidney disease (%)	50	50	p=1
Tubulointerstitial nephritis (%)	42.9	57.1	p=0.89

Discussion

There are no randomized controlled trials that examine treatment strategies and optimal levels of BP in RTRs to prolong graft survival or limit the risk of cardiovascular events. Therefore, the guidelines on the treatment of hypertension in RTRs in the last decades have been based on physicians/transplant units, individual efficacy, tolerability and medical comorbidity. In our study, the majority of RTRs were invariably treated with BB (66.3-82.50%) followed by CCB, the usage of which was reduced constantly year by year (63.4%-52.8%). Approximately one third of RTRs were treated with ACEI or ARB, and its usage did not change significantly. The analysis also indicates a slight increase in the percentage of patients who received diuretics and alfa-blockers in subsequent years. When patients only treated with monotherapy were taken into account, the drug distribution profile was quite similar, i.e. almost two thirds of RTRs were treated with BB, and only around twelve percent used CCB as a single antihypertensive agent. These results differ from reports provided by

other centers in which CCBs were the most often administered medications, e.g. in 80% of Polish subjects studied by Malyszko et al [4] and in 62.9% of Austrian RTRs studied by Tylicki et al [5]. The dominant role of CCB, often treated as first line hypotensive drugs in RTRs, is due to their demonstrated antihypertensive efficacy and their potential to counteract the vasoconstrictive effects of calcineurin inhibitors [6]. The use of CCB is also associated with earlier allograft function recovery. Whether this results in long-term graft protection is however, unclear [1].

Mortality after renal transplantation is still high, and cardiovascular complications are the leading cause of death in RTRs [7, 8]. RTRs usually have heightened activity of the sympathetic nervous system so therapy with BB may offer a survival benefit. Some observational reports showed that therapy with BB is associated with better long-term survival of RTRs [9]. These facts may have influenced the wide use of BB among our cohort of RTRs. One should remember, however, about possible metabolic side effects of BB such as dysglycemia and dyslipidemia to which RTRs are already prone, and an unexpected finding from this study, that BB use was inversely associated with achievement of target blood pressure.

Of note, the drug distribution profile in studied RTRs is also completely different when compared to the stage 1-4 CKD population from the same unit. As we reported previously, agents inhibiting renin angiotensin aldosterone system were the most commonly prescribed classes of antihypertensive drug in stage 1-4 CKD patients. In 2011, in our unit, 74% of patients received those drugs, with nearly 80% of CKD patients with proteinuria. ACEI are the most common, as approximately every other 1-4 CKD patient is treated with them [10]. In the Polish CKD population not managed by a nephrology clinic (PolNef analysis of 2007), approximately 61% of patients receive ACEI [11]. Although the use of ACEI and ARB has increased in the last decades in RTRs, their use is not as widespread as in CKD patients; probably due to the fear of the presence of renal artery stenosis in the graft, which is associated with the risk of acute renal injury. Moreover, many RTRs are people with stage 3b, 4 CKD who are particularly prone to deterioration of graft function, hyperkalaemia and the development of anaemia after treatment with ACEI or ARB. In contrast to patients with CKD of native kidneys, one should also note that the nephroprotective potential of ACEI or ARB, has not been confirmed in RTRs [12-17]. ACEI or ARB were prescribed only for approximately 40% RTRs, therefore, similar to that reported by others [4, 18].

Thiazide diuretics are often used as the initial treatment of hypertension in the general population. As we reported previously stage 1-4 CKD patients receive diuretics almost twice as often as RTRs from the same unit [10]. Diuretic therapy coupled with salt restriction may cause a drop in glomerular filtration because of the impaired capacity of hemodynamic adaption of the transplanted kidney, it is this knowledge which may have resulted in some concerns over the frequent usage of diuretics in RTRs [19]. Moreover, thiazide diuretics can cause electrolyte disorders, dyslipidaemia and may increase serum uric acid, which is an independent predictor of cerebrovascular or cardiac events [20].

Our study showed that all RTRs who required antihypertensive treatment did receive it. A significant increase was observed in the mean number of antihypertensive drugs per patient in subsequent years (2.24 ± 1.03 in 2001 to 2.55 ± 1.25 in 2014). Of note is that, a higher number of antihypertensive agents was positively associated with achievement of proper BP control. In large clinical studies, 3.5 drugs were needed on average to achieve optimum arterial BP values [14]. In turn, Malyszko et al. reported that RTRs required a minimum of three hypotensive drugs [4]. Similar to the studies by Premasathian et al. and Bulatova et al., the most common dual antihypertensive combination in our RTRs was BB with CCB [21, 22].

In the presented study, between 45.5 and 59.9% of RTRs reached the recommended values of BP in the covered years. This is in accordance with previous researches examining BP control in RTRs. In a retrospective cohort study by Kasiske et al. 48.7% of patients reached BP levels of $<140/90$ mmHg [3]. In another study conducted in France 42% of RTRs had controlled hypertension [23]. The quality of treatment received is also quite similar to

the one observed for 1-4 CKD patients from the same unit, and almost twice as good as that of the general population as noted in the latest NATPOL 2011 study analysing treatment of hypertension in Poland [10, 24]. Although the treatment quality increased up to 2011, a slight deterioration of BP control was observed between 2011 and 2014. One may assume that the release of new recommendations in the JNC 8 Report in 2014, which raised the target BP for CKD patients from 130/80 to 140/90 mmHg might have influenced clinical practice in our unit and the results of the final survey [25]. Moreover, discussions over the results of the ONTARGET study in 2011 cast doubt on the idea of aggressive BP control, as it led to beneficial effects in stroke prevention, but not for myocardial infarction, heart failure, or overall cardiovascular events, especially in the high risk population – for instance the RTRs. Furthermore, we cannot exclude the influence of the rearrangement of our treatment team between 2011-2014 as a major bias and a reason for the drop in achieving BP target values.

In the presented study, patients were more likely to achieve target BP if they were younger and used a higher number of antihypertensive agents. The study also confirmed the important negative association between allograft dysfunction and BP control [22]. RTRs with higher eGFR were more likely to achieve target BP. The negative association between diagnosis of primary glomerulonephritis or hypertensive nephropathy and BP control was observed as well. We also, cannot exclude that the improvement of BP control between 2001-2011 in our study was associated (next to the intensification of treatment) with some changes in the studied population over time e.g. decrease of mean age of patients and decreasing percentage of subjects suffering from primary glomerulonephritis.

There are some limitations to the study. Firstly, the use of office BP readings, often done once, to monitor the quality of BP control may be subject to significant error due to the white-coat syndrome. In reality therefore, treatment results may be even better. In addition, the assessment of antihypertensive treatment effectiveness was based on a retrospective analysis of causal BP measurements, frequently following the morning dose of medications, which can significantly reduce the mean value of BP. Secondly, the surveys, in fact, were not performed on the same patients, and therefore there is the possibility that observed changes were dependent on differences in demographic and clinical characteristics between patients enrolled. Only 96 patients were present in all four analyses. However, despite the limitations, the study highlights some important information for the RTR community regarding the need for further improvement in the quality of management of hypertension.

Conclusion

The study showed the intensification of treatment of hypertension in RTRs in successive years with BB assuming the dominant role.

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Disclosure Statement

No potential Disclosure Statement was reported by the authors.

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