Comparison of early and long-term impact of percutaneous transluminal renal artery angioplasty alone or with brachytherapy on renal function in patients with reno-vascular hypertension

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Abstract

Background: Renal ischaemia resulting from stenosis of the renal artery may result in two important sequelae: systemic arterial hypertension, and renal atrophy and nephron loss, resulting in an increased risk of progression to end-stage renal disease. Renal artery stenosis (RAS) may lead to both renovascular hypertension and ischaemic nephropathy – a potentially curable cause of renal failure.

Aim: To assess the efficacy of γ-intraluminal brachytherapy (ILBT) in prevention of restenosis after percutaneous transluminal renal artery angioplasty (PTRA) and the effects of this method of revascularisation on renal function.

Methods: 71 patients aged 52±8 years with refractory renovascular hypertension were randomised to group I (PTRA + ILBT) or group II (PTRA). Both baseline and 9-month follow-up angiography, intra-vascular ultrasound and non-invasive examination were performed to assess the efficacy of PTRA on renal function.

Results: The overall PTRA success rate was 87%: 33 patients from group I and 29 from group II underwent a successful procedure. A decrease of serum creatinine level was observed regardless of the treatment modality, directly after angioplasty: 20 µmol/l (17.5%) in group I and 26 µmol/l (22%) in group II (NS). Also in long-term follow-up this effect was sustained: 18 µmol/l (15.8%) in group I and 10 µmol/l (8.5%) in group II (NS). In the follow-up period a non-significant increase of serum creatinine level was observed in group I (from 94±19 to 96±25 µmol/l, NS). In group II the increase of serum creatinine level was significantly higher (from 92±39 µmol/l to 108±60 µmol/l, p=0.001).

Conclusions: PTRA improves renal function in patients with ischaemic nephropathy. In long-term observation the positive effect of PTRA on renal function is especially visible in patients with ILBT after PTRA.

Key words: brachytherapy, renal artery stenosis, atherosclerosis, percutaneous transluminal renal angioplasty

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Introduction

The opinion that clinical consequences of renal artery stenosis (RAS) should be considered in two aspects as either a cause of reno-vascular hypertension (RVH) or a factor contributing to the development of ischaemic nephropathia, a potentially reversible cause of renal failure, has gained importance in recent years [1, 2]. It is estimated that RAS occurs in 8 to 17% of patients with end-stage renal failure and in approximately in 17% of cases the artery is completely occluded [3-5]. It was shown that renal failure patients undergoing successful renal artery revascularisation leading eventually to normal blood flow restoration and improved glomerular filtration rate (GFR) may not require further therapy with dialysis [6, 7]. Both renal blood flow (RBF) and GFR are evaluated by means of clearance of various exo- and endogenous substances – creatinine and cystatin, respectively. In clinical practice creatinine clearance may be calculated using the Cockcroft and Gault formula [8]. A method still considered useful in RVH treatment, particularly in the elderly and individuals with concomitant chronic disorders, is percutaneous transluminal renal artery

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angioplasty (PTRA) followed by stent implantation or brachytherapy. Up to now, only a limited number of reports have described the use of brachytherapy in the treatment of RAS [9-12].

The aim of the present study was to asses the impact of PTRA with or without brachytherapy on the restenosis rate and renal function [13].

Methods

This study involved consecutive patients with atherosclerotic RAS who met protocol inclusion and exclusion criteria.

The study protocol received the approval of the Bioethical Committee of the Silesian Medical University in Katowice (No. 330/99 dated 26.05.1999). Patients with no contraindications to angiography at age ≥40 years with stenosis of the renal artery lumen ≥50% caused by atherosclerotic lesions and clinical signs suggesting RVH refractory to medical therapy, patients at risk for renal failure development due to progressive ischaemia with diameter of stenotic artery ≥3 mm were selected. A diagnosis of atherosclerotic RVH was established during hospitalisation of patients in the Chair and Department of Nephrology, Endocrinology and Metabolic Disorders of SUM in Katowice. The PTRA procedures were performed in the Catheterisation Laboratory of the Silesian Heart Disease Centre in Zabrze. Gamma irradiation was carried out in the Brachytherapy Department, Institute of Oncology in Gliwice using the self-centring Paris® Catheter System. First, the degree of RAS was assessed in the angiographic examination that employed QCA calculations, then patients who fulfilled angiographic inclusion criteria were randomly assigned to one of two groups using two sealed and numbered envelopes. Two days prior to PTRA procedures, patients received 150 mg of Aspirin and 250 mg of Ticlopidine (both *p.o.*), and just before angioplasty 10 000 IU of heparin (*i.v.*). Moreover, they were continued on therapy with antiplatelet agents.

According to the study protocol, 9 months after angioplasty repeat hospitalisation was planned to carry out control follow-up renal artery angiography, intravascular ultrasonography (IVUS) and other non-invasive examinations.

Criteria of successful procedure

Early and long-term procedural efficacy was evaluated on the basis of degree of stenotic lesion dilatation in the angiographic examination, and presence or absence of signs of restenosis at the site of dilated stenosis during follow-up. PTRA was considered successful if the residual stenosis did not exceed 30% of the lumen of the dilated artery. In the long-term follow-up PTRA was considered successful if there was no significant restenosis. Stenosis recurrence was defined as when stenosis was equal to or exceeded 50% of the arterial lumen at the site of the previously dilated lesion (significant restenosis).

The impact of the procedure on protection of renal function based on serum creatinine concentration assessment and calculated value of glomerular filtration rate were examined. A decrease or stabilisation in both creatinine concentration and GFR after the procedure was considered as procedure success. Lack of changes in the values of creatinine concentration and GFR in the follow-up were regarded as achievement of renal function stabilisation.

Intravascular brachytherapy

A Nucletron microSelectron HDR device with step Ir^{192} source using a compatible self-centring PARIS catheter designed and developed by the Guidant company were employed for intravascular brachytherapy. The baseline activity of iridium source was approximately 10 Ci. Presupposed value of the referential isodose was 15 Gy, 2 mm from the surface of the centring balloon, thus in the adventitia area. Time of source stop at the consecutive points was calculated by a physicist in the system of therapy management to achieve the planned dose at the appropriate distance from the source axis. Mean radiation time was 3 min. (range from 1.5 to 4.5 min).

Statistical analysis

Continuous parameters with normal distribution are expressed as mean ± standard deviation. Significance of the differences between means was examined with Student's t-test. In the case of distribution other than normal Mann-Whitney U test was employed. Qualitative parameters were compared using the Chi-square test (additionally with Yates' correction in cases of less than 5 expected numbers within a given group). Spearman nonparametric correlation method was employed to evaluate the correlation between continuous parameters. A p value <0.05 was accepted as statistically significant. All calculations and statistical analyses were done using the statistical software package Statistica PL version 5.5 (StatSoft Inc.).

Results

Overall PTRA procedure success rate in the group of 71 patients (43 men and 28 women, mean age 52±8 years) who underwent randomisation was 87.3% (62 patients). The findings of renal artery angiographic evaluation in 33 patients randomly selected to group I (PTRA supplemented by brachytherapy) and 29 patients from group II (PTRA without brachytherapy) did not show any significant differences.

Follow-up angiographic assessment

The mean period to the repeated hospitalisation to perform follow-up control renal artery arteriography and other non-invasive examinations consistent with the study protocol was 294 days in group I and 319 days in group II. During

follow-up 4 patients died, 3/62 (4.8%) patients from group I and 1/29 (3.5%) subject from group II (NS).

At the end of follow-up, 59 (95.2%) patients underwent control examination that involved 31 (93.9%) of group I and 28 (96.5%) patients from group II.

Long-term angioplasty efficacy was higher in the brachytherapy group. In group I restenosis was detected in 4 (12.9%) patients compered with 9 (32.9%) from group II ($p < 0.05$). In the angiographic assessment the loss of artery lumen was 1.16±0.73 mm in group I while in group II it was significantly larger (1.71±0.67 mm; p=0.0037).

Impact of PTRA procedure of renal failure development

Serum creatinine concentration in both examined groups was similar before (114±30 µmol/l in group I and 118±83 µmol/l in group II, NS) and after PTRA (94±19 µmol/l, 92±39 µmol/l, NS). Mean creatinine concentration dropped directly after PTRA by 20 µmol/l (17.5%) in group I and by 26 µmol/l (22%) in group II (NS), and at the end of follow-up by 18 µmol/l (15.8%) in group I and 10 µmol/l (8.5%) in group II (NS). In the period between PTRA and the last follow-up examination, a slight, non-significant increase in creatinine concentration to 96±25 µmol/l (NS) was observed in group I, in contrast to group II, where a more pronounced, statistically significant elevation of creatinine level to 108±60 µmol/l (p=0.001) was observed.

A significant increase in GFR values was observed after PTRA in both examined patient groups. Within the period between PTRA and the last follow-up examination, a slight but non-significant decrease in GFR among patients from group I was observed, in contrast to patients from group II, who manifested a significant drop in GFR value (p=0.001) (Figures 1 and 2).

Group I and II patients did not differ with respect to GFR either before or directly after PTRA. However, in the follow-up GFR in group I patients tended to be higher (p=0.07) (Figures 1 and 2). Recurrence of renal artery stenosis, which was observed more frequently in group II, was associated with a decrease in GFR value. A significant negative correlation between the degree of RAS and GFR in the follow-up means that a higher percentage of RAS was associated with a lower GFR (r=–0.51; $p < 0.001$).

Discussion

The clinical success of PTRA is assessed not only as normalisation or improvement in medical control of arterial hypertension but also as stabilisation and improvement in excretory renal function [14-19].

The advantages of improved renal artery patency rate following PTRA depend on the degree of perfusion restoration within viable nephrons. The lack of a precise marker of revascularisation procedure efficacy makes a comparative analysis of the studies in the various centres difficult [19]. It is commonly accepted that revascularisation should be considered successful if creatinine concentration decreases by at least 20%. However, those who regard as success maintenance of creatinine concentration after the revascularisation procedure (stabilisation of renal excretory function) stress achieved improvement in perfusion of the renal parenchyma and inhibition of loss of active nephrons. A meta-analysis of 10 studies performed by Isles et al. [20] that included observations of 148 patients after PTRA with stent implantation documented improvement or stabilisation of renal excretory performance in 74% of patients. Similarly, Watson et al. [4] noted improved renal excretory function

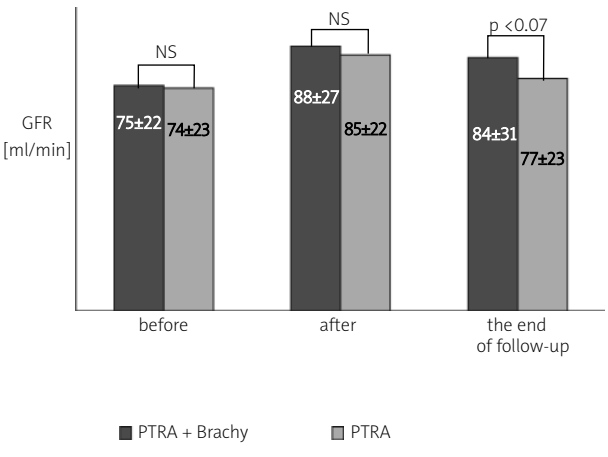

Figure 1. A comparison of GFR between group I and II in the consecutive points of measurements

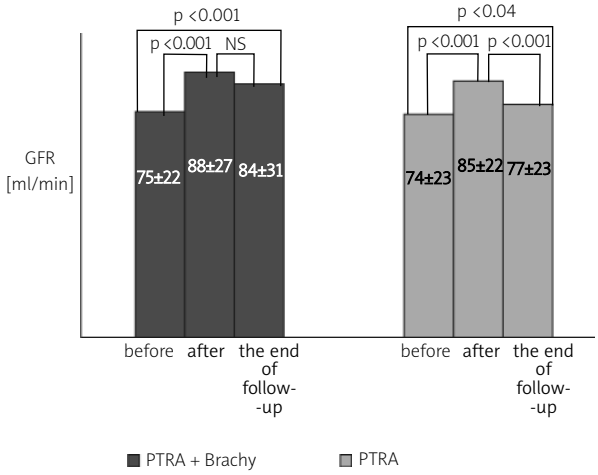

Figure 2. A comparison of GFR within both group I and group II in the consecutive points of measurements

in 72% of patients after angioplasty procedures done in 33 patients with bilateral RAS or artery stenosis of only one active kidney. In the remaining 28% of subjects, serum creatinine level indicated functional stabilisation of the kidneys. However, Blum et al. and White et al. did not reveal any marked changes in serum creatinine concentration after angioplasty procedures completed by stent implantation [13, 25]. The above-mentioned meta-analysis of Isles et al. also indicates slow and progressive increase in serum creatinine level throughout follow-up [20].

In our study, more benefits (a decrease in creatinine concentration during follow-up) were seen in the group of patients with additional brachytherapy. After a decrease in creatinine concentration was achieved, as noted in the group of patients with PTRA followed by brachytherapy, its level during follow-up again increased progressively in 50% of patients and was found to be higher than the upper normal limit, but in none of them was it higher than prior to the procedure. In the group of patients who did not undergo brachytherapy, a recurrent increase in creatinine level was noted in 75%. These findings require confirmation in other clinical trials due to the limited number of subjects in the study group. Also, the analysis of GFR revealed that it increased following invasive treatment of RAS in most reports. Rooden et al. noted significant ($p < 0.01$) elevation of the mean values of GFR following surgical correction of stenosis [18]. The GFR increase in the analysed groups of patients after PTRA was similar. The GFR value during follow-up in the groups was slightly ($p=0.073$) higher in patients with brachytherapy that followed angioplasty. Similar results were presented by Pickering et al. after 2-year follow-up of 55 cases [21]. Also observation in Mayo Clinic confirmed no adverse changes with respect to GFR values within 2-year follow-up [22]. Unfortunately, a favourable outcome after angioplasty was not supported by the results of three prospective randomised clinical trials [17, 23, 24]. No significant changes in the serum creatinine level in patients after PTRA were noted. The inconsistent findings of the aforementioned studies may have resulted from variable selection of the relatively small groups of examined patients as well as the chronic nature of the disease. Chronic reno-vascular hypertension may lead to secondary non-reversible morphological changes such as vascular remodelling followed by progressive stiffness of the arterial wall with functional alterations of the vascular endothelium. The introduction of anti-platelet drugs to routine management with patients before and after PTRA and the opportunity to use low-osmolar dye markedly increased the safety and efficacy of this method and also limited the number of thromboembolic complications and contrast related renal injury.

The results of our study confirmed the efficacy of angioplasty procedures followed by brachytherapy in restoration of normal flow in the renal artery and improvement in active renal parenchyma perfusion. Revascularization procedure failure may have resulted from advanced renal parenchyma fibrosis and other concomitant disorders (e.g. hypertension-induced nephropathia). Chronic ischaemia leads not only to injury of the renal parenchyma but also provokes adaptive renal changes in response to low perfusion pressure. Unfortunately, in these cases, restoration of the physiological flow may even worsen renal function and intensify proteinuria.

Conclusions

Percutaneous angioplasty of the stenotic renal artery improves renal perfusion assessed by means of GFR both during in-hospital stay and the follow-up period. Brachytherapy potentialies these favourable effects by limitation of restenosis development.

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Porównanie wczesnej i odległej skuteczności zabiegu przezskórnej angioplastyki zwężonej tętnicy nerkowej z następczą brachyterapią lub bez niej u chorych z nadciśnieniem naczyniowo-nerkowym

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Streszczenie

Wstęp: Zwężenie tętnicy nerkowej pod względem następstw klinicznych należy rozpatrywać w dwóch aspektach: jako przyczynę nadciśnienia naczyniowo-nerkowego oraz jako czynnik odpowiedzialny za rozwój nefropatii niedokrwiennej.

Cel: Celem pracy była ocena wpływu przezskórnej śródnaczyniowej angioplastyki tętnic nerkowych z brachyterapią lub bez niej na częstość występowania restenozy po zabiegu przezskórnej angioplastyki oraz na czynność nerek.

Metody: Do badania włączono 71 chorych (43 mężczyzn i 28 kobiet) poddanych randomizacji, u których wykonano zabieg przezskórnej angioplastyki zwężonej tętnicy nerkowej (ang. *percutaneous renal-artery angioplasty*, PTRA). Do grupy I – PTRA z brachyterapią, zakwalifikowano losowo 33 chorych, do grupy II – PTRA bez brachyterapii – 29 chorych. Po 9 miesiącach zaplanowano ponowną hospitalizację w celu wykonania kontrolnej angiografii tętnicy nerkowej oraz pozostałych badań nieinwazyjnych.

Wyniki: Spadek stężenia kreatyniny po zabiegu PTRA w grupach I i II był podobny, wynosił odpowiednio 20 µmol/l (17,5%), 26 µmol/l (22%) i nie różnił się statystycznie (NS), podobnie jak w obserwacji odległej – 18 µmol/l (15,8%) w grupie I i 10 µmol/l (8,5%) w grupie II (NS). W obserwacji odległej w grupie I zaobserwowano niewielki wzrost stężenia kreatyniny z 94±19 do 96±25 µmol/l (NS), natomiast w grupie II nastąpił istotny statystycznie wzrost stężenia kreatyniny z 92±39 do 108±60 µmol/l (p=0,001).

Wnioski: Przezskórna angioplastyka zwężonej tętnicy nerkowej wpływa na poprawę perfuzji nerek. W obserwacji odległej efekt ten jest szczególnie widoczny u chorych, u których po PTRA zastosowano brachyterapię.

Słowa kluczowe: brachyterapia, miażdżyca, przezskórna śródnaczyniowa angioplastyka tętnic nerkowych

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