TRATAMENTO ENDOVASCULAR DE ESTENOSE DE ARTÉRIA DE TRANSPLANTE RENAL: RESULTADOS À CURTO E MÉDIO PRAZO

ENDOVASCULAR MANAGEMENT OF TRANSPLANT RENAL ARTERY STENOSIS: EARLY AND MID-TERM RESULTS

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RESUMO

OBJETIVOS: A disfunção de enxerto renal e agravamento de hipertensão nos pacientes transplantados renais podem ser manifestações de hipoperfusão do enxerto devido a estenose de artéria de transplante renal (EATR) ou estenose da artéria ilíaca proximal à anastomose do enxerto (pseudo-EATR). O tratamento endovascular de EATR é cada vez mais frequente para manter a função do enxerto. Com este estudo, pretendemos avaliar o impacto do tratamento endovascular de EATR na função renal a curto e médio prazo.

MATERIAIS E MÉTODOS: Este é um estudo observacional, retrospectivo, monocêntrico que inclui todos os pacientes transplantados renais adultos submetidos a tratamento endovascular de EATR entre Setembro de 2017 e Junho de 2020. A função renal foi monitorizada através da medição da creatinina sérica (sCr).

RESULTADOS: Treze pacientes foram incluídos (53.8% do sexo feminino), com idade média de 57 (21-70) anos. Onze pacientes (84.6%) desenvolveram disfunção de enxerto. Dez pacientes (76.9%) foram submetidos a angioplastia transluminal e colocação de stent na artéria renal do enxerto e três (23.1%) da artéria ilíaca dadora. A maior parte dos casos (69.2%) foram tratados durante o primeiro ano pós transplante. A taxa de sucesso técnico foi de 100%, sem mortalidade periprocedimento. A taxa de morbidade aos 30 dias foi de 15.4%. O tempo médio de seguimento foi de 20.2 (1.3 – 36.3) meses. Um doente morreu durante o seguimento e outro sofreu agravamento de disfunção do enxerto com necessidade de hemodiálise e nefrectomia. A redução na sCr foi estatisticamente significativa no primeiro mês pós-intervenção, comparado aos valores pré-intervenção, mas a sCr continuou aumentada quando comparado aos níveis basais (pré-diagnóstico de EATR).

CONCLUSÃO: A maioria dos pacientes (12/13) melhorou ou estabilizou a função renal após a intervenção em relação ao período pré-intervenção, mostrando a eficácia do procedimento. No entanto, a maioria dos doentes desenvolveu reestenose. O atraso no diagnóstico de EATR pode comprometer o benefício da revascularização e impedir a recuperação total da função renal.

Palavras-chave
Estenose de Artéria de Transplante Renal (EATR); Cirurgia Endovascular

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ABSTRACT

OBJECTIVE: Renal graft dysfunction or worsened hypertension in renal transplanted patients may be a manifestation of graft hypoperfusion due to transplant renal artery stenosis (TRAS) or stenosis of iliac arteries proximal to renal transplant (pseudo-TRAS). Endovascular management of TRAS has been increasingly used to preserve renal graft function. With this study, we aim to evaluate the impact of endovascular treatment of TRAS on renal function in the short to medium term.

MATERIAL AND METHODS: This is an observational, retrospective, single-center study that included all adult renal transplant patients who underwent endovascular intervention on TRAS between September 2017 and June 2020. Renal graft function was monitored by serum Creatinine (sCr) levels.

RESULTS: Thirteen patients were included (53.8% female), with a median age of 57 (21-70) years. Eleven patients (84.6%) presented with graft dysfunction. Ten subjects (76.9%) underwent transluminal angioplasty and stenting of renal artery and three (23.1%) of donor iliac arteries. Most cases (69.2%) were interventioned in the first-year post-transplant. Overall technical success was 100%, with no periprocedural deaths. Overall 30-day morbidity was 15.4%. Median follow-up time was 20.2 (6.3 – 36.3) months. One patient died during follow up and other worsened graft dysfunction, requiring hemodialysis and nephrectomy. Reduction in sCr levels was statistically significant in the first postoperative month, compared to preoperative values, but sCr levels were still increased when compared to baseline levels (pre-TRAS diagnosis).

CONCLUSIONS: The majority (12/13) of patients showed improvement or stabilization of renal graft function compared to the preoperative period, during the follow-up period, supporting the procedure’s safety. Despite this, most patients did not recover baseline sCr levels, reinforcing the importance of prompt graft revascularization. Delayed diagnosis of TRAS may compromise the benefit of revascularization and prevent full recovery of renal function.

Keywords
Transplant Renal Artery Stenosis (TRAS); Endovascular Surgery

INTRODUCTION

Renal transplantation (RT) is the treatment of choice for patients with end-stage renal disease offering better long-term survival and improved quality of life when compared to other forms of renal replacement therapy (RRT)[1]. Although transplant rejection still remains the most common complication after RT, vascular complications such as transplant renal artery stenosis (TRAS), occur in up to 23% of renal transplant recipients[2-3].

Renal artery stenosis (RAS) assumes greater importance in RT, as it occurs in a solitary denervated kidney where hypoperfusion does not directly elicit sympathetic activation, leading to chronic graft ischemia[3,4]. Prolonged renal ischemia may result in irreversible ischemic changes and self-perpetuating hypertension, that may persist even after an effective revascularization. TRAS is recognized as a potentially treatable cause of post-transplant arterial hypertension, allograft dysfunction, graft loss and premature death of the recipient[4,5,6], and there are now specific strategies focused on its prevention, early diagnosis, and effective treatment[2,4,5,6].

TRAS occurs more frequently in the first two years after RT but can develop at any time. It presents with severe refractory hypertension and/or graft dysfunction, in the absence of transplant rejection, ureteric obstruction, or infection[4]. Proximal iliac artery stenosis, mimics RAS, presenting with the same clinical manifestations (pseudo-TRAS)[1,2,4]. Different etiologic factors have been identified, such as flawed surgical technique, postoperative periarterial fibrosis, host immune response, infectious complications, long cold ischemia time, atherosclerosis, trauma, and chronic rejection[4,6]. Treatment options include percutaneous transluminal angioplasty (PTA) / stent placement or direct surgical revascularization, with the endovascular approach being preferable[4,5,6]. However, not all patients will benefit from treatment: the risk of vascular injury and graft loss must be balanced against the benefit of revascularization[4]. In clinically significant stenosis and/or stenosis superior to 50% on US-color-doppler, an “intent-to-treat” angiogram is performed, with a low risk of contrast induced kidney graft impairment[4,5,6].
Evolution of endovascular surgery allowed for more options in the treatment of TRAS. PTA was, initially, the first option, with placement of bare metal stent (BMS) being reserved for selected cases, such as refractory stenosis, dissection and restenosis. Many studies have demonstrated its effectiveness at restoring allograft perfusion and improving allograft function, but also an incidence of restenosis of 20 to 40%. Balloon angioplasty combined with BMS placement lowered the recurrence incidence to 10-20%, with some authors suggesting this procedure as first choice treatment. More recently, drug-eluting stents (DESs) showed lower rates of restenosis in the treatment of coronary artery disease (CAD), but studies comparing PTA, BMS and DES in TRAS are still insufficient and inconclusive.

With this paper, we report our experience of endovascular management of TRAS and pseudo-TRAS, and the outcomes of functional allograft improvement in the short and medium term.

**MATERIAL AND METHODS**

**Study Description**
This observational, retrospective study was conducted in a tertiary university hospital center. All clinical data of surgical procedures performed between September 2017 and June 2020 were reviewed and patients submitted to endovascular intervention (EI) of renal transplant artery or iliac arteries proximal to renal graft were selected. All adult patients (age ≥ 18 years) in clinical follow-up after renal transplantation, who were submitted to endovascular management of TRAS or pseudo-TRAS in this period, were included.

Relevant demographic, periprocedural, and follow-up data were retrospectively obtained from individual patient’s digital clinical file. The electronic file contains all the data used in this study, given the integration in the same software of clinical records from external consultation and hospitalizations, laboratory and imaging results, surgical data and drug prescription.

The following data were collected: demographic information (age, gender, medical comorbidities, smoking history), imaging and laboratory results (peak systolic velocities, estimated percentage of stenosis, serum Creatinine (sCr), estimated glomerular filtration rate (eGFR)), specificities of the EI (type of access, intervention, stent and contrast used); postoperative morbidity and mortality; and follow-up evaluation (need for secondary interventions, variation in graft function, need for RRT, renal transplant allograft failure and need for transplant nephrectomy).

Given the observational retrospective nature of the study, the written informed consent of the patients involved was waived.

The primary endpoint of this study was to analyze the impact of EI on TRAS/pseudo-TRAS in graft function, by measuring the variation of postoperative sCr at 1, 3 and 12 months after procedure compared to preoperative sCr levels.

Secondary endpoints were analysis of complications, need for nephrectomy or RRT, graft and patient survival and analysis of variation of postoperative sCr level (at 1, 3 and 12 month) compared to the baseline sCr level. Baseline sCr was defined by mean value of the best three consecutive sCr results in the first month after kidney transplantation.

For data analysis and comparison, a 10% variation in sCr was considered physiological daily variation. All data were introduced in a database and descriptive analysis was performed. The Kolmogorov-Smirnov test for normality was applied to assess normal distribution. For numerical variables, a non-parametric approach was used, using Mann-Whitney test to compare means. Medians with a minimum and maximum range (min-max) were calculated for continuous variables. The statistical analysis was performed with SPSS version 20.0 (IBM Corp., SPSS Statistics, Armonk, NY, USA) and a p-value < 0.05 was considered statistically significant.

**Evaluation protocol before renal transplantation**
Before renal transplantation, all patients undergo vascular evaluation comprising a complete medical history and physical examination, arterial and venous US-color-doppler to exclude iliac venous thrombosis and peripheral arterial disease. Further investigations including computed tomography angiography (CTA) are included if necessary for a better vessels’ characterization.

**Follow-up protocol after renal transplantation**
In our center all renal transplant patients undergo renal US-color-doppler after surgery. After hospital discharge, clinical follow-up is performed by dedicated nephrologists.

Vascular surgery team referral due to suspicion of TRAS is based on clinical criteria such as uncontrolled hypertension or unexplained graft dysfunction, after ruling out other frequent causes. US-color-dopplers are performed by a radiologist experienced in renal grafts evaluation. Peak systolic velocities greater than 200cm/s are considered suggestive of stenosis.
Protocol of intervention

All patients with US-color-coppler suggestive of stenosis undergo “intent-to-treat” arteriography and, if stenosis greater than 50% is confirmed, angioplasty with stent placement is performed. For arteriography and EI, different types of nonionic contrast (Visipaque®, Ultravist®, Optiray®) are used, preferably in low concentrations, obtained by dilution. After puncture of the ipsilateral common femoral artery and administration of 2000-3000 units of unfractionated heparin, the arterial lesion is carefully crossed, using a hydrophilic guidewire. Stent diameters are chosen according to the size of the normal artery immediately adjacent to the stenosis and selected to be equal to or 1 mm greater than this vessel segment. In cases of more significant stenosis, artery pre-dilation with balloon angioplasty is performed. Different types of stents are used according to the affected artery and availability: self-expanding stents Zilver Flex™ (Cook Medical, Bloomington, IN) and Absolut Pro™ (Abbott Vascular, Santa Clara, CA) are used in the external iliac arteries; balloon expandable stents Visipro™ (Medtronic, Minneapolis, MN) in common iliac arteries and Omega™ (Boston Scientific Corporation; Natick, MA, US) and Hippocampus™ (Medtronic, Minneapolis, MN) in renal arteries. Technical success is assumed if residual stenosis is less than 30%. Patients remain hospitalized overnight after EI in order to facilitate prompt identification and treatment of possible complications. Therapy with aspirin is initiated after the procedure. Patients’ clinical follow-up is performed by the transplant medical team.

RESULTS

Thirteen patients had significant (>50%) lesions on angiography and underwent EI. Participants’ median age was 57 years (21-70) at the time of the procedure and 7/13 (53.8%) were female. None of the patients had history of CAD, and only two had cardiac disease (moderate aortic stenosis and dysrhythmia – atrial fibrillation). None of the patients was a current smoker, with 3/13 (23%) being former smokers. Most patients (12/13; 92.3%) received deceased donor graft, 4 of which (33.3%) with expanded criteria. Primary indications for TRAS investigation were an increase in sCr of ≥20% from baseline (11/13; 84.6%) and structural abnormalities identified on posttransplant noninvasive imaging studies (2/13; 15.4%). Most cases that presented with graft dysfunction (9/11; 81.8%) had chronic/incipient graft dysfunction and two presented acutely with need of hemodialysis. 84.6% (11/13) of patients were diagnosed during clinical out-patient follow-up and elective arteriography and intervention was performed. Patients with acute graft dysfunction underwent hospitalization and urgent intervention. Only one patient performed arteriography before US-color-doppler, due to the availability of this procedure.

Arteriography identified ten cases (10/13; 76.9%) of renal artery stenosis, two (2/13; 15.4%) of external iliac artery stenosis (upstream of anastomosis) and one (7.7%) of primitive iliac artery thrombosis (occlusion). Angioplasty with balloon-expandable stent placement in the renal artery was performed in ten patients, and angioplasty with self-expandable stent placement in the external iliac artery (2/13) in two. In the case of common iliac artery thrombosis, recanalization with a hydrophilic guide-wire was performed, followed by bilateral angioplasty and balloon-expandable stent placement (“kissing stent”). Most interventions (12/13) were performed using percutaneous ipsilateral femoral access, except for the kissing stent, which was performed using percutaneous bilateral femoral access. The median time between transplantation surgery and EI was 8.36 (2.3-148.4) months. Most cases (9/13; 69.2%) were intervened in the first-year post-transplant. One patient presented as acute graft dysfunction due to iliac thrombosis 12 years after transplantation surgery. Overall technical success was 100%. There were no periprocedural deaths. Overall 30-day morbidity was 15.4% (2/13). There were two access-related complications: a groin hematoma that was surgically drained and a common femoral artery false aneurism treated with eco-guided thrombin embolization. No acute kidney injury related to contrast occurred in the cohort.

TABLE I summarizes sCr levels before and after intervention.

The median increase in sCr levels in the 3 months prior to the intervention compared to baseline levels was 1,67, 1,72 and 1,81 mg/dl, which corresponds to 20%, 33% and 33% respectively. When comparing preoperative sCr levels to baseline levels, there was a median increase of 1,05 mg/dl, which corresponds to 8% and 1% and was statistically significant. Postoperative sCr levels at 1, 3 and 12 months, compared to preoperative levels, had a median decline of -0,8, -0,7 and -0,75 mg/dl, which corresponds to -34%, -30% and -32% respectively. There was a statistically significant reduction in postoperative sCr levels at 1 month compared to preoperative levels (p = 0,028).

There was a median increase in postoperative sCr levels at 1, 3 and 12 months compared to baseline level of 0,22, 0,23 and 0,24mg/dl, which corresponds to 18%, 19% and 19% respectively.
Median follow-up time was 20.2 (1.3; 36.3) months. No patient required multiple interventions or had confirmed restenosis. One patient died during follow-up (1.3 months after intervention) due to unknown causes, with functioning graft. One patient worsened graft dysfunction due to chronic rejection, requiring RRT and transplant nephrectomy (7.6 and 16 months after procedure, respectively). Two patients did not complete 12 months of follow-up at data collection point. Overall primary patency rate at 12 months after EI was of 100%.

**DISCUSSION**

It is estimated that untreated TRAS raises the risk of graft loss by 2.8-fold. However, currently there are no prospective controlled studies to definitively answer if TRAS should be treated and which treatment would have a beneficial effect[6,7,10]. Recently, Patel et al[11] presented a retrospective study in which 41 patients who underwent endovascular treatment of TRAS were compared to a match control group of transplant recipients without this diagnosis over a period of 21 years (mean, 10.6 years). Long-term graft and patient survival were found to be statistically similar to those patients with no history of TRAS, with no difference in the number of patients needing RRT due to graft failure. This study may have important implications in solidifying the rationale and management of endovascular intervention for TRAS.

Many studies have shown superiority of endovascular over open surgery, the latter being reserved for patients considered unsuitable for radiological angioplasty (due to recent transplant, kinking, multiple or long stenosis) or after angioplasty failure[4,8,12,13,21]. There are a few studies comparing balloon angioplasty to use of stents in TRAS treatment, favoring primary use of stents for their lower rates of restenosis, although they are all retrospective studies with small cohorts[3,14,16-19]. In our series we have used BMS in treatment of TRAS and pseudo-TRAS and our results support endovascular surgery as a feasible and safe treatment option with a high rate (100%) of technical success, no rate of restenosis and zero 30-day graft loss and mortality. Complication rate was nearly 16% higher than described in literature[4,10,11,12,18]; however, all complications were minor and solved during the one-day hospitalization for the procedure. No major complications (dissection, thrombosis or rupture) were reported. The median elevation of preoperative sCr level compared to the baseline was 81% (± 666). This data includes two patients referred for anatomical changes in post-transplant US-color-doppler (without graft dysfunction) and two patients with acute graft dysfunction requiring RRT, justifying the lower and upper values, respectively. During postoperative follow-up there was a decrease in sCr levels of -34% at 30 days, -30% at 3 months and -32% at 12 months when compared to preoperative levels. Given that an increase in sCr up to 10% was considered physiological daily variation, all patients that maintained follow up showed improvement or stabilization of renal function in the postoperative period comparing to preoperative levels. These encouraging results suggest a beneficial effect of
the EI in slowing down graft dysfunction, which is consistent with previous published results. However, only 4 patients (30.8%) showed improvement or stabilization of renal function in the postoperative period compared to baseline values. These findings may be explained by the presence of irreversible ischemic changes in renal function caused by chronic hypoperfusion, since there was already a median increase in SCR levels of 20%, in the 3 months prior to EI. These findings enhance the importance of prompt investigation and intervention when TRAS is suspected. The present study based on real-world management of arterial complications of renal transplantation reinforces the importance of the follow-up programs post-kidney transplantation with early detection of TRAS or pseudo-TRAS and the efficacy and safety of endovascular management with low rate of complications.

Our study has several limitations such as its retrospective nature and heterogeneous characteristics of cohort, unequal clinical follow-up times, small sample size and lack of a control group.

CONCLUSION

Our results are consistent with those reported in literature and support the safety and efficacy of endovascular treatment of renal hypoperfusion caused by TRAS / pseudo-TRAS. All patients showed improvement or stabilization of renal function in first month compared to preoperative period, supporting the safety of this procedure. However, only 30.8% improved or stabilized their renal function in relation to their baseline SCR levels. This suggests irreversible chronic changes in renal function caused by hypoperfusion and reinforces the importance of prompt investigation and intervention when TRAS is suspected, since later diagnosis may compromise the benefit of revascularization and prevent full recovery of renal function.

REFERENCES


