ORIGINAL ARTICLE

REMOTE DONOR PRECONDITIONING FOR INCREASING TRANSPLANT SURVIVAL IN THE RECIPIENT'S BODY DURING THE KIDNEY TRANSPLANTATION FROM THE LIVING-RELATED DONOR

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ABSTRACT

The aim: To estimate the protective effect of remote ischemic preconditioning (RIPC) on kidney transplants harvested from living related donors.

Materials and methods: To achieve the claimed aim, there were examined 60 donor-recipient couples, where kidney transplant donors were living-related. All donors had the same anaesthetic management. The first group (n = 30) received RIPC which included four procedures of cuff inflations each lasting 5 minutes followed by 5-minute intervals of cuff deflation to measure blood pressure up to 40 mm Hg above systolic blood pressure on the shoulder. Patients of the second group (controls) did not experience RIPC (n = 30) and control group without RIPC.

Results: RIPC resulted in a statistically significant ($P<0.05$) increase in GFR of the transplanted kidney from 66±5 mL /min to 63±4 mL /min after 3 months, from 69±3 mL /min to 61±5 mL /min after 6 months, from 63±2.5 mL /min to 57±3 mL /min after 12 months; a 3-fold reduced partial delay of graft function; a 2-fold decreased incidence of acute kidney transplant rejection times; 1.5-fold decline in the incidence of primary non-function; and 1.4-fold tCr50 acceleration ($p = 0.16$). The follow-up period lasted for a year after transplantation.

Conclusions: RIPC during organ harvesting improved graft ischemic protection and increased functioning efficiency in the recipient.

KEY WORDS: renal ischemia, kidney transplantation, ischemia-reperfusion injury, remote ischemic preconditioning

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INTRODUCTION

Currently, kidney transplantation (KT) is the only radical treatment for end-stage renal disease (ESRD). For long-term renal replacement therapy, dialysis is an alternative to KT. However, the former is less patient-friendly and more costly compared with KT that ensures higher quality of human life (in physical, emotional, social, spiritual and financial aspects) [1-6].

Over the past few decades, KT has shifted from a risky experimental approach in the management of chronic renal failure (CRF) to a safe and life-saving measure. KT provides the full rehabilitation, including return to full-time employment, school, university, sports activity, family integration, and the ability to have children [2,5].

While performing an audit of health insurance claims data in the Netherlands, Mohnen S.M. et al. analysed the average annual healthcare costs associated with renal replacement therapy (RRT) by dialysis (in-centre haemodialysis, home haemodialysis, continuous ambulatory peritoneal dialysis, automated peritoneal dialysis and multiple dialysis modalities) per year of treatment and two transplant modalities (kidney from living and deceased donor). The total average annual healthcare costs in 2014 ranged from €77,566 for continuous ambulatory peritoneal dialysis patients to €105,833 for patients on multiple dialysis modalities, whereas costs for kidney transplant recipients were €85,127 in the year of transplantation and rapidly declined in the first and second year after successful transplantation (respectively €29,612 and €15,018); transplantation with a deceased donor kidney resulted in higher costs (€99,450) in the year of transplantation compared to living donor kidney transplantation. Due to the complexity of the calculation, such studies and calculations have not been conducted in Ukraine. However, there is evidence that after successful transplantation, annual costs decline substantially to a level that is approximately 14-19% of annual dialysis costs [4,5].

Renal ischemic reperfusion injury (IRI) is the key factor that affects survival of transplant experiencing ischemia from the moment it is cut off the donor blood supply during nephrectomy until the completion of renal artery anastomosis in the recipient. Leveling such an effect can enhance transplant function and improve the quality and life expectancy of the recipient eventually. The search for methods of protection and preservation of the graft at the stage of organ harvesting from a living family donor, including

modifying anaesthesia techniques, is relevant. As of today, according to various observations, there is no unambiguous view or solution to this problem. Apart from IRI prevention strategies, such as improved organ harvesting and preservation technologies, as well as reducing the period of cold and warm ischemia, remote ischemic conditioning (RIC), which is a new and promising approach to reduce postoperative renal IRI, has attracted much attention in recent years. Given the fact that offered techniques differ in the execution time within the perioperative period and actual conditioning methods, the efficacy of this option of preventing IRI remains debatable. Based on the execution time, RIC can be classified into three types: remote ischemic preconditioning (RIPC) which is induced before the target organ experiences ischemia; remote ischemic perconditioning induced during ischemia of the target organ, but before reperfusion; remote ischemic postconditioning induced in the time of reperfusion initiation [2, 3, 7-11].

THE AIM

To study the efficacy of the original remote ischemic preconditioning to increase the probability of survival of kidney transplants from living-related donors during anaesthesia.

MATERIALS AND METHODS

To achieve the above aim, there were examined 60 living-related kidney donors who received anaesthesia during kidney transplantation. They were divided into two groups: RIPC group (n = 30) and control group without RIPC (n = 30). RIPC was performed after anaesthesia before donor nephrectomy. The original RIPC protocol included four procedures of cuff inflations each lasting 5 minutes followed by 5-minute intervals of cuff deflation to measure blood pressure (BP) up to 40 mm Hg above systolic blood pressure on the shoulder.

All patients had the same anaesthetic management. Anaesthesia was induced with intravenous fentanyl 2-3 μg/kg, esmeron 0.6 mg/kg and propofol 2 mg / kg body weight. Supportive anaesthesia was maintained with fentanyl 1-2 μg / kg / h, esmeron 0.1-0.2 mg / kg / h and sevoflurane at age doses with 0.8 to 1.2 target minimum alveolar concentration (MAC). The depth of anaesthesia was monitored with the use of bispectral index (BIS) technology (BIS VISTA monitor, Aspect Medical Systems, USA); the target range of BIS values was 40-60. Additional measurements during anaesthesia, including ECG, pulse oximetry, capnography, blood pressure, central venous pressure (CVP), body temperature, hourly urine output , and the calculation of fluid balance at all stages of surgery, were performed using Dräger Primus® workstation (Dräger Medical, Germany).

Apart from the routine parameters of renal concentrating and excretory abilities, including acid-base balance, blood and urine biochemistry, etc., RIPC efficacy analysis was based on the parameters as follows:

1. Glomerular filtration rate (GFR), which was calculated with the modification of diet in renal disease (MDRD) equation at 0, 1, 2, 3 days after transplantation, and prior to discharge from hospital if needed [12,13].
2. An incidence of acute renal allograft rejection, which was monitored within the first year of follow-up. Acute rejection was defined by decreased renal function requiring treatment, it was biopsy-confirmed.
3. Partial delay of graft function, which was determined within the first week after transplantation. The need for dialysis in the first week following transplantation was the criterion for this condition [14].
4. An incidence of primary non-function within the first 3 months after transplantation, which was defined as a permanent lack of kidney graft function.
5. Time to a 50% decrease in baseline creatinine (tCr50).

Statistical processing was performed with IBM SPSS Statistics 23 software package. The Mann-Whitney U-test was used to compare differences between groups when the data were not normal distributed. Fisher's exact test was utilized to analyse the categorical data. Values of $p \leq 0.05$ were considered significant. We presented mean values with standard deviation and the median with 25th and 75th percentiles or n (%). The effect of the type of intervention on GFR, when observed at 3, 6 and 12 months after transplantation, was determined using a linear mixed-effect model.

The criteria for inclusion in the study were as follows: end-stage renal disease, age ≥ 18 years, ABO blood group compatibility of the donor-recipient pair. The exclusion criteria included age of patients under 18 years, ABO blood group incompatibility of the donor-recipient pair.

The follow-up period lasted for a year after transplantation.

The transplantation procedure was performed by four transplant surgeons selected at random pursuant to standard protocols, and they were not different with regard to the qualification. The immunosuppression was routine and included intravenous induction of basiliximab and methylprednisolone or oral prednisolone and oral triple maintenance therapy with calcineurin inhibitors, mycophenolate mofetil and prednisolone.

RESULTS

Donors and recipients in the two study groups were comparable with regard to age, sex, body weight, anaesthesia risk assessment score on the scale of the American Society of Anaesthesiologists (ASA), GFR, and intraoperative donor's characteristics (Table I). Glomerulonephritis, diabetes mellitus, and autoimmune diseases predominated among the primary medical conditions that had contributed to kidney damage (Table II). Cardiovascular comorbidities (mainly arterial hypertension) were noted in most recipients of both study groups (Table III). There was no difference in some intraoperative parameters between the groups (Table III).

After three months following KT, graft function was better in the RIPC group: GFR was statistically significantly higher

Table I. Characteristics of donors and recipients.

Parameters	Donors	
	Group with no RIPC (n=30)	RIPC group (n=30)
Age (years)	54 ± 9	53 ± 13
Male (n (%))	15 (50)	14 (46)
BMI (body mass index) (kg/m^2)	26.1 ± 3.7	27.4 ± 3.3
ASA I/II	21/9	22/8
GFR (mL/min)	113 ± 21	116 ± 25
Smoking (n (%))	10 (33)	11(36)
MAP (mean arterial pressure) (mm Hg)	94 ± 9	95 ± 10
	Recipients	
	n=30	n=30
Age (years)	39 ± 15	42 ± 11.5
Male (n (%))	17 (56)	15 (50)
BMI (kg/m^2)	26.1 ± 3.2	25.2 ± 3.8
ASA II/III	17/13	15/15
MAP (mm Hg)	106 ± 11.1	100 ± 15.3

Table II. CRF-underlying medical conditions in the recipient (n - number of cases)

Diabetes	5	6
Autoimmune diseases	5	7
Glomerulonephritis	7	5
Multicystic dysplastic kidney	3	5
Tubulointerstitial nephritis	2	3
Others	8	4
Cardiovascular comorbidities (n[1] (%))	25 (83)	28 (93)

[1] - number of cases

(p = 0.028) than in the control cohort (66.0 ± 4.6 ml / min versus 63.4 ± 3.8 ml / min, respectively). This pattern persisted at 6 months after KT: GFR in the RIPC group was statistically significantly higher (p = 0.0001) than the corresponding value in controls (68.7 ± 3.3 ml / min versus 61.1 ± 5.3 ml / min, respectively). Improved GFR tended to remain at 12 months after KT (63.4 ± 2.5 ml / min versus 57.4 ± 3.3 ml / min, respectively) (Table IV). Furthermore, there was seen a tendency to a reduced incidence of partial delay of graft function from 10% (3 patients) to 3% (1 patient) (p = 0.612) in the RIPC group. Similar trends were recorded for the incidence of acute renal allograft rejection - a decrease from 20% (6 patients) to 10% (3 patients) (p = 0.236), the incidence of primary graft non-function – a decline from 15% (5 patients) to 10% (3 patients). The offered RIPC technique also contributed to a decrease in tCr50 on average from 120 to 96 hours (p = 0.16). (Table V). Statistical insignificance of the data may be related to the small number of patients in each group at the time of the study.

GFR

GROUP WITHOUT RIPC

3 months (63.4 + 3.8) and 6 months (61.1 + 5.3), adjusted mean difference, 2.3 (95% CI, - 0.6-5.2), p = 0.18.

3 months (63.4 + 3.8) and 12 months (57.4 + 3.3), adjusted mean difference, 5.9 (95% CI, 3-8.8), p = 0.0001.

6 months (61.1 + 5.3) and 12 months (57.4 + 3.3), adjusted mean difference, 3.7 (95% CI, 0.8-6.6), p = 0.009.

RIPC GROUP

3 months (66.0 + 4.6) and 6 months (68.7 + 3.3), adjusted mean difference, 2.6 (95% CI, 0.3-5), p = 0.026.

3 months (66.0 + 4.6) and 12 months (63.4 + 2.5), adjusted mean difference, 2.7 (95% CI, 0.3-5.1), p = 0.021.

6 months (68.7 + 3.3) and 12 months (63.4 + 2.5), adjusted mean difference, 5.3 (95% CI, 3-7.7), p = 0.0001.

DISCUSSION

While studying a model of acute myocardial infarction in dogs more than 30 years ago, Murry C.E. et al. (1986) [12,15] 5demonstrated that the previous compression of the circumflex artery with subsequent reperfusion contributed to the higher resistance of the myocardium to prolonged ischemia and reduced the further size of the experimental infarct site by 75%. Later on, this event was termed "ischemic preconditioning". Furthermore, in vivo studies showed that this condition was universal, occurring

Table III. Some intraoperative indicators of the quality of anaesthesia of the donor and recipient.

Parameter	Donor	
	Group without RIPC (n=30)	RIPC group (n=30)
Perioperative fluid volume (mL/ kg)	57.8 ± 12.3	60.0 ± 11.1
BIS	48±7	45 ± 6
MAP (mm Hg) the moment of kidney harvesting	89 ± 9	87± 17
Blood test at the time of kidney harvesting		
pH	7.41 ± 0.03	7.39 ± 0.04
Lactate (mmol /L)	1.5 ± 0.4	1.7 ± 0.7
	Recipient	
	Group without RIPC (n=30)	RIPC group (n=30)
Graft ischemia time (min)[1]	205 ± 29	217 ± 32
Perioperative fluid volume (mL/kg)	55.9 ± 13.0	58.2 ± 17.8
BIS	42 ± 7	46 ± 7
MAP (mm Hg) at the time of kidney connection to the blood flow	92 ± 12	85 ± 8
Blood test at the time of kidney connection to the blood flow		
pH	7.35 ± 0.04	7.32 ± 0.05
Lactate (mmol /L)	1.4 ± 0.4	1.7 +0.6

Note: [1] - Graft ischemia time (min) is the period from the moment of kidney harvesting from the donor's body to the moment of inclusion of the kidney in the recipient's body.

Table IV. Evaluation of the recipient's graft function.

Parameter	Group without RIPC (n=30)		RIPC group (n=30)			
Follow-up periods	N	M+SD	N	M+SD	Difference of means (95% CI)	p
GFR						
3 months after KT	25	63.4+3.8	27	66.0+4.6	2.7 (0.3-5.0)	0.028
6 months after KT	25	61.1+5.3	27	68.7+3.3	7.6 (5.1-10)	0.0001
12 months after KT	25	57.4+3.3	27	63.4+2.5	5.9 (4.3-7.6)	0.0001

• The effect of the type of intervention on GFR, when observed at 3, 6 and 12 months after transplantation, was determined using a linear mixed-effect model.

in all biological beings [16,17,19-21]. What is more, it is characteristic not only of the myocardium, but also other organs to increase the tolerance to ischemia when exposed to ischemic preconditioning. [22-24]. While preparing kidneys for IRI in animal models, Wever K. E. et al. found that a similar effect could be achieved by remote ischemia-reperfusion to the site of vascular surgery - remote preconditioning [25-28].

The advances in surgery, anaesthesiology and intensive care promote the empowerment of KT introduction, which is currently considered as a treatment of choice for end-stage renal disease, compared with dialysis. Ischemic preconditioning is a promising method of additional protection and preservation of the graft at the stage of organ harvesting from a living related donor. However, the efficacy of this method is ambiguous for a number of reasons, including different protocols of the method, limited sample size and severity of renal transplant patients (age, comorbidities, drugs used), etc. [1, 9,11, 18, 20].

This study showed that remote preconditioning, which included four procedures of cuff inflation while measuring blood pressure on the shoulder up to 40 mm Hg above systolic blood pressure followed by 5-minute intervals of cuff deflation to achieve sublethal ischemia, resulted in a statistically significant (P <0.05) increase in GFR of the transplanted kidney: from 63.4 ± 3.8 mL / min to 66.0 ± 4.6 mL /min after 3 months, from 61.1 ± 5.3 mL /min to 68.7 ± 3.3 mL /min after 6 months, from 57.4 ± 3.3 mL / min to 63 ± 3 mL /min after 12 months; a 3-fold reduction in partial delay of graft function; a 2-fold decrease in the incidence of acute kidney transplant rejection times); 1.5-fold decline in the incidence of primary non-function; and 1.25-fold tCr50 acceleration (p = 0.094). The mechanisms of possible beneficial effects of conditioning are still being investigated. Two temporal phases of protection are assumed: early (occurs within a few minutes and lasts up to 4 hours) and late (occurs after 24 hours and lasts up to 72 hours). The key mechanisms of the early phase are related to the mediators that are released during hypoxia. They initiate a cascade of

Table V. Assessment of recipient's graft function.

Parameter	Group with no RIPC	RIPC group
Partial delay of graft function (n (%))	3 (10%)	1 (3.3%), [1] (p = 0.612)
Incidence of acute renal allograft rejection (n (%))	6 (20%)	3 (10%), [1] (p = 0.236)
Incidence of primary non-function (n (%))	5 (16%)	3 (10%), [1] (p = 0.353)
	Me (25%; 75%)	
tCr50	120 (72; 132), n = 30	96 (56; 120), n = 30 U = 338, [2] (p = 0.094)

Note: [1] - Fisher's exact test was used to analyse the categorical data. Values of p ≤0.05 were considered significant.
[2] -The Mann-Whitney U-test was employed to perform the analysis of numerical data (tCr50). Values of p ≤0.05 were considered significant.

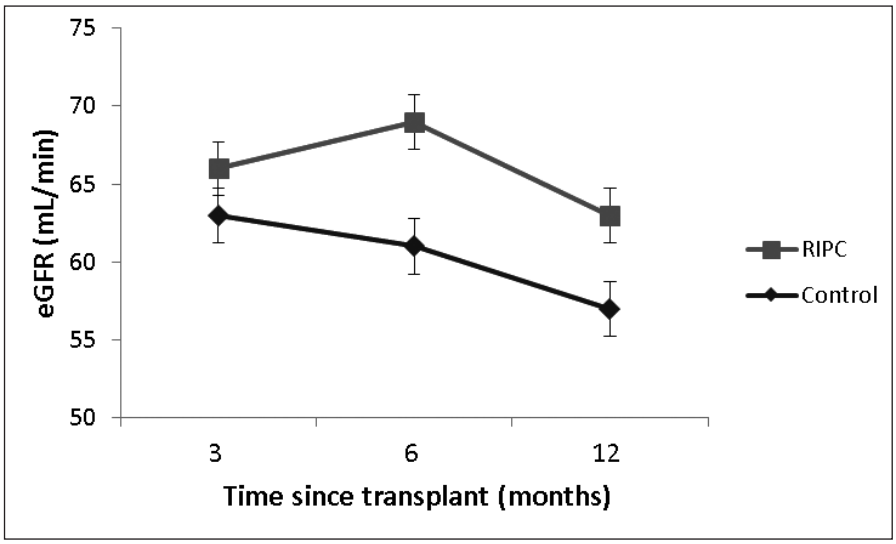

Fig. 1. Influence of remote ischemic preconditioning (RIPC) on glomerular filtration rate (GFR) at 3, 6 and 12 months of follow-up. The diagram, which is based on a linear mixed- effect model, demonstrates the marginal mean GFR values in each group with regard to the time of determination. The error bars show the +/- 1 standard error of the marginal means.

protection, involving the activation of G-protein-coupled receptors, promoting the induction of protein kinases (phosphatidylinositol-4,5-bisphosphate-3-kinase), extracellular signal-regulated kinase, mitogen-activated protein kinase, protein kinase C, etc. In turn, they activate potassium-dependent ATP channels in mitochondrial membranes, which results in blocking the permeability of membrane pores, hindering the flow of ions through those channel, including calcium ions, thus preventing the rupture of mitochondria and cell death (apoptosis). The late phase is associated with the regulation of the synthesis of anti-apoptotic and anti-inflammatory genes by humoral (accumulation of adenosine, opioids, endocannabinoids, bradykinin, CGRP and stromal cell-derived factor-1α, etc.), neuronal (stimulation of efferent nerves that protect the organ) and systemic (generation of systemic anti-inflammatory / anti-apoptotic genomic responses through regulation of anti-inflammatory gene synthesis and inhibition of leukocyte activation) pathways. Among them, it is the latter that is to a greater extent associated with remote preconditioning [16, 17, 29-34].

CONCLUSIONS

Kidney transplantation (KT) is currently the treatment of choice for end-stage renal disease, compared with a lifetime on dialysis. Therefore, the search for techniques that can empower the protection of donated kidneys from ischemic injuries is of utmost importance. The use of the original RIPC method including the induction of four procedures of sublethal ischemia, which was achieved with cuff inflation followed by 5-minute intervals of cuff deflation while measuring blood pressure on the shoulder up to 40 mm Hg above systolic blood pressure, made it possible to improve the anti-ischemic protection of the graft and increase the efficacy of its functioning, namely a statistically significant increase in GFR was found at 3, 6 and 12 months after transplantation; there was also seen a clinical decrease in the incidence of partial delay in graft function, acute allograft rejection, and primary non-function. RIPC is a safe, patient-friendly and low-cost technique that facilitates the accelerated and improved kidney transplant function, and can thus extend the life of a transplanted kidney. Even though the evidence for the effect of RIPC on our endpoints was weak, possibly due to the small number of patients and the dependence of the clinical effect of RIPC on the recipient's general condition and concomitant pathology, etc., there is strong evidence of clinically significant improvement in renal function after transplantation.

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